HEALTH NOTES

Women's Health

Consumer Education and Communication Committee

Dedicated to building bridges of communication with those Californians whose health depends on proper drug therapy, compliance with a treatment regimen and a healthier lifestyle.

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Health Notes

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Women's Health

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Introduction

HEALTH NOTES is published by the California State Board of Pharmacy's Consumer Education and Communication Committee to assist California pharmacists and other healthcare providers to be better informed on subjects of importance to their patients.

This issue of *HEALTH NOTES* addresses the area of women's health.

One of the greatest triumphs of twentieth century medicine in the United Sates has been the dramatic increase of human longevity. For females, this extended life span is even more dramatic than for men. Outliving their male counterparts, on the average, a minimum of seven years, females now account for well over fifty percent of the U.S. population.

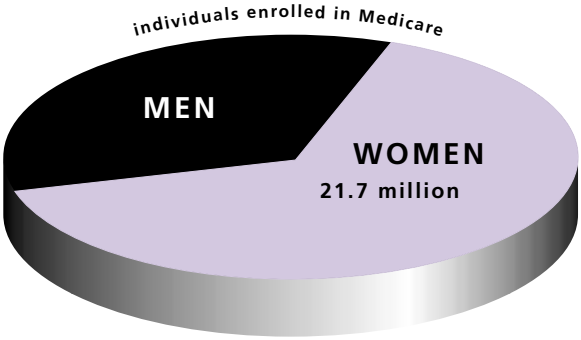
Females' longer life expectancy, combined with the overall aging of the population, indicates that women's health issues will become increasingly important.

It is not surprising that many of the questions asked pharmacists involve some aspect of women's health. Females are vulnerable to virtually all of the diseases that affect men, plus a host of additional concerns. From puberty onward, many women will experience: menstrual problems including premenstrual syndrome, infertility challenges and the health problems that can accompany pregnancy, yeast infections, cervicitis, pelvic inflammatory disease, fibroids, endometriosis, ovarian cysts, urinary tract infections, and menopause, including the complications related to osteoperosis.

In addition to most forms of cancer that men face, women also confront the dangers of breast cancer, cervical cancer, ovarian cancer, and endometrial cancer. Fully a third of all females over the age of 65 suffer from cardiovascular disease, with nearly half a million women a year dying from this illness.

Pharmacists can have a valuable influence on the health care of women by assisting them in properly managing their medications and by ensuring that their drug therapy outcomes are effective.

We anticipate that this issue of *HEALTH NOTES* will be a valuable resource in helping pharmacists and other health care providers to communicate important information about women's health issues to their patients.



Women account for $95 billion in Medicare spending annually.

source: HCFA, 1996

M. Standifer Shreve
Editor, Health Notes
Chair, Consumer Education and Communication Committee

PHARMACIST AND OTHER HEALTH CARE PROVIDER

GUIDE TO THE

Risk Assessment of Drugs in Pregnancy and Lactation

By Ronald J. Ruggiero, Pharm.D.
Clinical Professor, Pharmacist Specialist in Obstetrics and Gynecology
Departments of Clinical Pharmacy and Obstetrics, Gynecology and Reproductive Sciences
University of California, San Francisco, Schools of Pharmacy and Medicine.

Learning Objectives: After reading these articles, participants should be able to:

FOR PREGNANCY AND LACTATION:

- Outline the steps a pharmacist should take to assess risk factors of medications when taken by pregnant women.
- Outline the steps a pharmacist should take to assess risk factors of medications when taken by breastfeeding women.

Medications in Pregnancy

Step One: Review the Outcomes Data Concerning Human Pregnancy

Approximately 18% of human pregnancies end in miscarriage, and more than 17,000 California infants are born with birth defects each year. According to the California Birth Defects Monitoring Program 1983-1990, 50 of the 1,600 babies born every day in California have birth defects. The cause of most defects is unknown. Of the 50 infants affected, about five will not survive, eight have heart defects, three have oral clefts, two have Downs syndrome, and one has a neural tube defect. Since 15% of all US births occur in California, this program serves as a national benchmark.[1]

Approximately 3%, or one in 33 of the 1.6 million births monitored in California from 1983-1990 involved an infant with a serious structural defect. Fifty five percent of infants with birth defects had two or more malformations (see Tables 1, 2 and 3).[1]

TABLE 1

Overall Incidence of Structural Defects

Heart	1 in 200
Cleft lip and/or cleft palate	1 in 550
Pyloric stenosis	1 in 550
Down syndrome	1 in 900
Neural tube defect	1 in 1400
Limb defect	1 in 1750

TABLE 2

55% of Infants with Birth Defects Will Have Two or More Malformations

Muscles, skeletal system	38%
Eyes, ears, face	33%
Heart, circulatory system	21%
Genitals, reproductive system	18%
Digestive system	15%
Central nervous system	14%
Respiratory system	14%
Kidneys, urinary tract	8%
Other abdominal organs	5%

Step Two: Be Aware of the Value of Preconceptional Counseling and Early Post-Exposure Intervention

Since more than 50% of US pregnancies are unplanned and many of these are unintended, it is very important that women of childbearing age be screened for potential hazards to the fetus. Such screening should include (1) genetic screening (e.g., for sickle cell, Tay-Sachs, B-thalassemia, or cystic fibrosis); (2) serological status of rubella, HIV and hepatitis B, when appropriate; (3) an assessment of work and environmental hazards, such as exposure to potentially toxic chemicals or sources of radiation; (4) risk assessment of prescription and over-the-counter drugs, alcohol, nicotine, and caffeine; and (5) risk assessment of illnesses such as diabetes and phenylketonuria. In addition, women should be instructed to take the recommended daily folic acid supplement (0.4 mg per day).[2]

Contrary to popular belief, most exposures to potential teratogens (drugs or other agents that cause abnormal development) do not result in birth defects. However, if prompt and adequate counseling concerning the risks of a drug exposure is not available, many mothers will choose to terminate their pregnancies. Once informed that the actual risk to their baby is small, most women decide to continue their pregnancies. The Motherisk Program in Toronto, Canada reported that of 78 women who had less than a 50% desire to continue pregnancy before being counseled, 61 decided to continue their pregnancies after consultation about first trimester exposure to drugs, chemicals, or radiation. After being counseled in early pregnancy, 84.5% of the women chose to continue their pregnancies, compared to 34.3% before counseling. Of the 17 who chose to terminate their pregnancies, only two had been exposed to teratogenic drugs. In most of the other cases, the pregnancy was terminated for reasons unrelated to the teratogen exposure.[3]

Step Three: Be Aware of the Labeling Laws Concerning the Fetal and Neonatal Risks of Drugs

The following risk in pregnancy categories have been assigned to drugs, either by the Food and Drug Administration or by the authors of books dealing with drugs in pregnancy:[4-7]

(1) Human studies conducted with the drug are negative for teratogenicity. The possibility of fetal harm appears remote.

(2) Either human studies have not been conducted and animal studies with the drug are negative for teratogenicity, or human studies conducted with the drug are negative for teratogenicity and animal studies are positive for teratogenicity.

(3) Human studies have not been conducted with the drug, and animal studies are positive for teratogenicity, or there are no human or animal studies. The drug should be given only if the potential benefit justifies the potential risk to the fetus.

(4) Human studies conducted with the drug are positive for teratogenicity, but the benefits of using the drug may outweigh the risks.

(5) Human and/or animal studies conducted with the drug are positive for teratogenicity, and the risks of using the drug outweigh the benefits. Contraindicated in pregnancy.

Several years after the risk in pregnancy categories were formulated, the Over-The-Counter Drug (OTC) Labeling Warning became required on all OTC medications that are systemically absorbed. It reads as follows: **AS WITH ANY OTHER DRUG, IF YOU ARE PREGNANT OR NURSING A BABY, SEEK THE ADVICE OF A HEALTH CARE PROFESSIONAL BEFORE USING THIS PRODUCT.**

Unfortunately, health care providers must contend with the dilemma that there is usually only animal and anecdotal human data about drug exposure during pregnancy, and such exposure is a recognized cause of less than 1% of congenital anomalies. Some expert dysmorphologists, after doing a thorough evaluation of the literature, concluded that the assignment of drugs to risk in pregnancy categories (1), (2), (3), (4) or (5) has no more accuracy than assignment by chance.

Step Four: Risk Assessment of Potentially Harmful Exposures

It is beyond the scope of this article to discuss specific drugs. Instead, the following steps are suggested to assess the potential for fetal harm resulting from an exposure during pregnancy.

(a) Obtain a medication history consisting of:

- The first day of the last menstrual period, to determine the gestational age at the time of the exposure. Gestational age indicates which organ(s) may have been affected.

TABLE 3

Selected Birth Defects

Rates per 1,000 births

Anophthalmia		0.1
Arthrogryposis		0.3
Bladder construction		0.2
Cataract		0.2
Chromosome defects (combined)		2.2
Down Syndrome	1.3	
Trisomy 18	0.2	
Trisomy 13	0.1	
Cystic kidney disease		0.3
Diaphragmatic hernia		0.3
Ear anomalies with hearing loss		0.4
Fetal alcohol syndrome (FAS)		0.1
Gastroschisis		0.2
Heart defects (combined)		4.9
Coarctation of the aorta	0.4	
Hypoplastic left heart	0.2	
Pulmonary atresia/stenosis	0.7	
Single ventricle	0.1	
Tetralogy of Fallot	0.4	
Transposition of the great vessels	0.5	
Truncus arteriosis	0.1	
Ventricular septal defects	1.8	
Holoprosencephaly		0.1
Hydrocephalus		0.5
Hypospadias		0.3
Imperforate anus		0.5
Intestinal atresia		0.4
Limb defects (combined)		0.5
Upper limb defects	0.4	
Lower limb defects	0.2	
Neural tube defects (combined)		0.7
Anencephaly	0.3	
Spina bifida	0.4	
Omphalocele		0.2
Oral clefts (combined)		1.7
Cleft lip w/wo cleft palate	1.1	
Cleft palate	0.6	
Pyloric stenosis		1.4
Renal agenesis (bilateral)		0.2
Tracheo-esophageal fistula		0.2

Source of Tables 1, 2 and 3: California Birth Defects Monitoring Program registry data, 1990-1994

There is a window of safety from the first day of the last menstrual period through two weeks postconception when harm is unlikely to occur to the fetus. Remember that it takes approximately four half-lives to clear a drug from the mother's body.

Exposure of the father to any agent has not been shown to be teratogenic.[8] However, the duration of the human spermatogenesis cycle is approximately 74 days. A conservative approach would be to wait 10-12 weeks (following four half-lives to clear the drug from the father's body) to avoid the potential effects of a drug on sperm.[9]

The following shows the timing of human development in relation to sensitivity to teratogens (postconception time shown in weeks):[10]

Forming part	High sensitivity to teratogens	Low sensitivity to teratogens
Central nervous system	3-6.5	6.5-32 postnatal
Heart	3-6.5	6.5-12
Ears	4-12	12-36
Eyes	4-12	12-36
Arms and fingers	4.5-7.5	7.5-8.5
Legs and toes	4.5-7.5	7.5-8.5
Genitalia	5.5-12	12-38
Teeth	6.5-10	10-36

Originally published in "Manual of Clinical Problems in Adult Ambulatory Care," 2nd edition, 1992. Reprinted with permission of Lippincott-Raven, Philadelphia, PA.

- The identification of all drug and chemical exposures:

  This should include prescription drugs, over-the-counter drugs, abused drugs, and environmental exposure. Also include the dose, route of administration, length of exposure, maternal states that may alter drug clearance, and maternal states that may pose a teratogenic risk.

(b) Evaluate the risk using the available resources which include:

- Drugs in Pregnancy and Lactation[5]
- Drugs in Pregnancy and Lactation Update[6]
- Shepard's Catalog of Teratogenic Agents[11]
- "Teratogenicity and Drugs in Breast Milk," Chapter 45, in the Sixth Edition of Applied Therapeutics: The Clinical Use of Drugs[4]
- "Drugs and Pregnancy" in the Eighth Edition of Handbook of Clinical Drug Data[8]
- Vendor Databases (i.e., MICROMEDEX, Inc.):[12]
  TERIS Teratogenic Information System[13]
  REPROTEXTTM Reproductive Hazard Reference
  REPROTOX Reproduction Hazard Information
  Shepard's Catalog of Teratogenic Agents[11]
- Note: The Physicians' Desk Reference will only give assigned pregnancy categories and is insufficient to assess risk.

(c) If sufficient information cannot be obtained from the literature or data bases:

- Call your local teratogen registry[14]
- Call your local pharmacist-operated drug information center[15]
- Call your local poison control center[16]
- Call the manufacturer's medical department[17]
- Refer the patient to a medical geneticist or to a dysmorphologist

Step Five: Presentation of Your Findings to Other Health Care Providers and the Patient

As discussed above, preconception counseling about fetal drug exposure is ideal. However, postconception counseling following an exposure is extremely important and can serve to reassure the expectant couple that the risks have been evaluated as thoroughly as possible. There is nothing worse than receiving differing risk assessments from several health care providers. Therefore, it is mandatory that the patient understands that the best information available has been found. If the pharmacist is answering questions directly for an expectant couple, it will be in their best interest to include the mother's other health care provider(s) so that a consensus can be reached about the risk. It should be emphasized that it is difficult to give an accurate risk assessment in most cases due to a general lack of data, but that the risk inherent to human reproduction of having a child with a major malformation is currently approximately 3% nationwide.

Medications in Lactation

Step One: Review the Basic Information on the Passage of Drugs into Breast Milk[4,18]

Information on the passage of drugs into breast milk and the effects on the infant is often scarce. When information is not found in the standard resources listed below, the manufacturer or a local drug information center may be helpful.

Certain precautions can be taken to minimize the effect of maternal medications on the nursing infant:

(a) The mother should wait to take the drug until immediately after breast-feeding.

(b) The infant should be observed for unusual signs or symptoms.

(c) Drugs that are safe when given directly to an infant and drugs that are known not to pass readily into breast milk are preferred to other agents.[10]

Step Two: Identify the Drug, Dose, Regimen, Duration, and Time of Exposure

Without discussing specific drugs, the following steps are suggested to assess the potential for harm of a given exposure to the breast-fed infant.

(a) Evaluate the risk using recognized resources. Recognized resources include:
- The Committee on Drugs, American Academy of Pediatrics, "The transfer of drugs and other chemicals into human milk,"[19]
- Drugs in Pregnancy and Lactation,[5]
- Drugs in Pregnancy and Lactation Update,[6]
- "Teratogenicity and Drugs in Breast Milk," Chapter 45 in the Sixth Edition of Applied Therapeutics: The Clinical Use of Drugs,[4]
- "Drugs and Breastfeeding" in the Eighth Edition of Handbook of Clinical Drug Data,[20] and
- Vendor databases (i.e., MICROMEDEX, Inc.): DRUGDEX System.[12]

(b) If sufficient information cannot be obtained from the literature or data bases:
- Call your local pharmacist-operated drug information center,[15]
- Call your local poison control center,[16]
- Call the manufacturer's medical department,[17] or
- Refer the patient to a lactation educator.

In summary, information is sparse on the effects of drugs both in pregnancy and lactation. Patients should be made aware of this and of the fact that birth defects occur in human reproduction even without exposure to teratogens. A comprehensive risk assessment using the steps outlined above and the references listed is essential. The patient must clearly understand the risks to the fetus or infant that are identified. Communication among all of the patient's health care providers regarding these risks is important to insure that the patient receives consistent information. Accurate and timely counseling on the risks of drugs in pregnancy or breast-feeding allows the patient to make a decision that is in the best interest of her fetus or infant. ■

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Contraception:

A Review of Current Methods

By Kathleen Hill-Besinque, Pharm.D., M.S.Ed.
Director, Professional Experience Programs
Assistant Professor of Clinical Pharmacy, University of Southern California School of Pharmacy

Learning Objectives: After reading this article, participants should be able to:

FOR CONTRACEPTION:
- Recognize factors which should be considered in the selection of a contraceptive method.
- Compare and contrast the various methods of contraception and the risks and benefits associated with each.
- List at least four non-contraceptive benefits of the use of oral contraceptives.

Introduction

Contraception choices are both personal decisions and public health issues. The personal aspects include issues related to sexuality, family plans, religious or cultural beliefs, medical conditions, and individual preferences. Public health issues include increases or decreases in the relative risk for cancers, medical complications of contraception and childbearing, and abortion rates. Although the availability, safety, and efficacy of contraceptive methods have been improved significantly over the past fifty years, the rate of unplanned pregnancies in the United States remains among the highest in developed countries.[1] An estimated fifty percent of all pregnancies in the United States are unplanned, and it is estimated that half of the unplanned pregnancies are aborted. Teen pregnancy contributes significantly to the unintended pregnancy rate in the United States. Unintended pregnancy rates are also high in women who are 40-44 years old, indicating a need for more contraceptive options for older women.

Misconceptions regarding contraceptive methods are common. A 1993 Gallup poll found that 65% of women believed that oral contraceptives were at least as risky as pregnancy. Actually, the risk of death from pregnancy is more than five times the risk of death resulting from oral contraceptive use in nonsmoking women. In fact, no contraceptive method carries more risk to women than pregnancy and childbirth. In the same survey, 58% of respondents were unable to name one noncontraceptive benefit of oral contraceptives. The survey found that 29% of women believed that oral contraceptives cause cancer, and 31% believed the contraceptive failure rate to be at least 10%. The same survey found that only 6% of respondents thought protection from some cancers resulted from oral contraceptives.[2]

Actually, there are several noncontraceptive benefits from oral contraceptives, including protection from ovarian and endometrial cancer. Despite educational programs, the prevalence of misconceptions regarding the risks and benefits of contraception remains high.

Role of Pharmacists

Pharmacists are in an ideal position to educate women about contraception and help them with contraceptive choices. Patient counseling and education improve contraceptive efficacy and patient satisfaction with contraceptive choices. Contraceptives, when used incorrectly, may result in an unplanned pregnancy or unwanted side effects. Side effects are a significant cause of non-compliance with contraceptive methods and discontinuation of use. Women may have fears about a method or questions about the printed information provided with oral contraceptives. The pharmacist is more accessible than other medical providers and is usually the provider of contraceptive products. Strategies to cope with side effects may improve compliance and continuation. Instructions regarding initiation of the regimens, missed pills, and back-up contraception can be provided when contraceptives are dispensed. In addition to prescription products, several contraceptive products are available over the counter. Patients using barrier methods of contraception such as diaphragms or condoms may be offered information about emergency contraceptive options. Questions regarding safety, techniques for proper use, and the efficacy of nonprescription products can be answered by the pharmacist.

Factors in Selection of Method

Many factors are considered in the selection of a contraceptive method. Patient concerns regarding the safety and efficacy of a method are important

determinants. Other factors include the desire for future pregnancy, age of the patient, experience with contraceptives in the past, the need for protection from sexually transmitted diseases, cultural and religious beliefs, partner cooperation, ability of the patient to properly use the method, and cost. Factors in the selection of a contraceptive also include medical conditions or contraindications to hormonal contraception, the potential for drug interactions, the need for episodic versus continual protection from pregnancy, and noncontraceptive benefits. Noncontraceptive benefits are becoming increasingly important in the selection of contraceptive methods. Factors important to the selection of contraceptive methods change over time. Women should be offered opportunities to reassess their contraceptive choices throughout their reproductive lives.

Failure Rates and Continuation Rates

Approximately half of all unplanned pregnancies occur in women using contraception.[1,3] All methods of contraception have an inherent failure rate. Contraceptive failure may occur because the method was not effective (method failure), because the patient did not use the method or did not use it properly (user failure), or as a result of interfering factors such as drug interactions. The efficacy of contraceptive methods is evaluated on the basis of perfect use and typical use data. Perfect use is derived from clinical trials in which highly motivated patients are using the method correctly and with complete compliance. Failure rates for perfect use are generally lower than rates reported during typical use. Typical use is the failure rate reported by actual patients under everyday circumstances.

Another important factor related to contraceptive failure is the continuation rate for contraceptive methods. A continuation rate is the percentage of users still using a method after one year. Continuation rates are influenced by contraceptive failure (pregnant patients no longer require contraception) and by patient dissatisfaction with the method. The most common reason for discontinuation of hormonal contraceptives is the occurrence of side effects (particularly breakthrough bleeding). Table 1 lists the typical use and perfect use failure rates, and continuation rates for contraceptive methods currently available in the United States.

Hormonal Contraception

Since the discovery that hormones control and regulate the menstrual cycle in the 1930s, researchers have worked to develop hormonal products that control fertility. Hormonal methods of contraception are safe, reversible, provide noncontraceptive benefits to users (and past users), and are highly effective. Contraindications

continued on page 45

TABLE 1

Effectiveness Use Rates in United States

Method	Reversible(Y/N)	Effectiveness* Perfect Use	Effectiveness* Typical Use	Continuation Rates**
Sterilization	Not reliably	High	High	High
Norplant™	Yes	High	Hig	High
Depo-Provera R™	Yes (May be a delay)	High	High	Moderate
Combination oral pills	Yes	High	High	Moderate
Progestin only pills	Yes	High	High	Moderate
Male condoms	Yes	High	Moderate	Moderate
Diaphragm	Yes	Moderate	Moderate	Moderate
Periodic abstinence	Yes	Moderate	Low	Moderate
Spermicides	Yes	Moderate	Low	Low
No method	NA	Low	Low	Low

* highly effective=less than 3% failure rate
moderately effective=failure rate 3-20%
low=failure rate greater than 20%

** high continuation rate=80% or more continuation after 1 year
moderate continuation rate=50-80% continuation after 1 year
low continuation rate=less than 50% continuation after 1 year

TABLE 2

Missed Tablets

Number of tablets missed	Action by patient	Back-up contraception required
1	Take missed tablet as soon as remembered. If not until the next day, take 2 tablets for one day only.	No (may be advised by some clinicians for 7 days)
2	Take 2 tablets as soon as remembered and take 2 tablets the next day.	Yes, for 7 days.
3	Begin a new cycle of pills using the instructions from the product insert (Sunday or first day of flow start).	Yes, until 7 days of therapy taken.

FIGURE 1

A.C.H.E.S.

Abdominal pain
Chest pain
Headache
Eye or vision changes
Severe leg pain

Difficult or Painful Menstruation (Dysmenorrhea)

Learning Objectives: After reading this article, participants should be able to:

FOR DYSMENORRHEA:
- Compare the differences between primary and secondary dysmenorrhea.
- List three OTC products used to treat primary dysmenorrhea.
- Identify three counseling pearls which should be shared when making OTC recommendations to patients.

By Leslie Shimp, Pharm.D., M.S.
Associate Professor of Pharmacy,
College of Pharmacy, University of Michigan
Consultant pharmacist, Department of Family Practice, Medical School,
University of Michigan

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Introduction

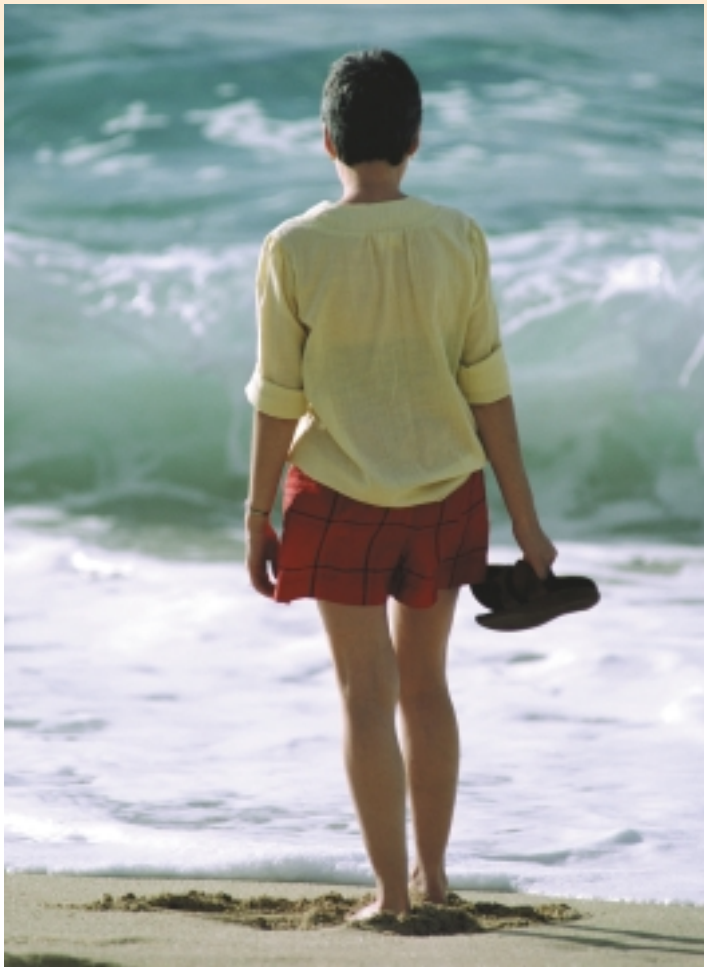
Nonsteroidal anti-inflammatory drugs (NSAIDs) are generally effective in 66-90% of women with primary dysmenorrhea. Several factors such as the dose, regimen, and side effects can influence patient response. Education concerning appropriate product selection, dosing, and side effect management is especially important for women on nonprescription NSAID therapy. This article provides information on the optimal use of over-the-counter (OTC) products for dysmenorrhea, as well as guidelines for identifying primary dysmenorrhea and the women for whom OTC therapy can be recommended.

Primary Dysmenorrhea

Dysmenorrhea, defined as difficult or painful menstruation, can be classified as primary or secondary disease.[1] Primary dysmenorrhea is characterized by pain and related symptoms that occur at the time of menstruation in the absence of identifiable organic pelvic pathology (e.g., endometriosis). The pain associated with primary dysmenorrhea is a cramping type pain in the lower midabdominal or suprapubic area. The pain may radiate to the lower back or upper thighs. Related symptoms include nausea, vomiting, diarrhea, headache, fatigue, nervousness and dizziness.[2] Symptoms usually begin at or shortly after the start of menses and last for about 48-72 hours.

Primary dysmenorrhea occurs most often in young women. It usually appears during adolescence or the early to mid-twenties and is less common past the age of 35 years. Primary dysmenorrhea occurs only during ovulatory cycles, and its prevalence increases from the early teen years to the late teens as the regularity of ovulation increases.[1,3] Prevalence declines in women older than 30 years, primarily due to the influence of pregnancy. During late pregnancy there is a decrease in uterine adrenergic nerves, and many do not regenerate after childbirth.[4]

Several characteristics distinguish primary dysmenorrhea from secondary disease. Secondary dysmenorrhea results from identifiable pelvic pathology, such as pelvic inflammatory disease, endometriosis, ovarian cysts, benign uterine tumors, endometrial cancer, and congenital abnormalities. Women are usually 30 years of age or older when this condition first appears, and symptoms are typically not confined to the two or three days at the beginning of menses (see Table 1).[5]



Primary dysmenorrhea is thought to be related to prostaglandin synthesis by the uterus. Prostaglandin levels in women with primary dysmenorrhea may be 5-13 times greater than those in women without dysmenorrhea. In addition, the symptoms of primary dysmenorrhea are similar to the symptoms produced by exogenous administration of prostaglandins.[1,3,6] In the uterus, prostaglandins cause contractions and vasoconstriction, sometimes resulting in uterine hypoxia (low oxygen) and pain.[3] Women with dysmenorrhea have greater contraction pressures during contractions, a longer duration of individual contractions, and a shorter time between contractions. Both intrauterine pressure and the number of contractions are related to dysmenorrhea pain.[1-3]

TABLE 1

Distinguishing Primary and Secondary Dysmenorrhea

	Primary	Secondary
Age at Onset	mid to late teens, early 20s	usually 30 years or older
Duration of Pain	begins at onset of menses and lasts 48-72 hours	not always linked to menses; may continue throughout menses or occur at other times in the cycle
Gynecologic Health	no pelvic pathology	history of irregular menstrual cycles, menorrhagia, pelvic inflammatory disease, infertility

TABLE 2

Nonprescription Drugs for the Treatment of Dysmenorrhea

NSAIDS	Availability	Recommended regimen
Ibuprofen (Motrin IB™, Advil™, Midol™, others)	200 mg tablet	1 tablet every 4-6 hours; may increase to 2 tablets if relief is not adequate (maximum dose per 24 hours: 1200 mg).
Naproxen Sodium (Aleve™)	220 mg tablet	1 tablet every 8-12 hours; an initial dose of 440 mg may improve effectiveness (maximum dose per 24 hours: 660 mg)
Ketoprofen (Actron™, Orudis KT™)	12.5 mg tablet	1 tablet every 4-6 hours; an initial dose of 25 mg may improve effectiveness (maximum dose per 24 hours: 75 mg)

Treatment Overview

NSAIDs and oral contraceptives are the principal drugs prescribed for the treatment of primary dysmenorrhea. In women who do not want to take oral contraceptives for birth control, NSAIDs are the drugs of choice. Currently, three NSAIDs are available as nonprescription products for the treatment of dysmenorrhea: ibuprofen 200 mg, ketoprofen 12.5 mg, and naproxen sodium 220 mg. These drugs should only be recommended to women with primary dysmenorrhea. A pharmacist can help a woman decide if self-treatment is appropriate by asking for her age and a description of symptoms, and ascertaining whether she has any medical conditions that may predispose her to secondary dysmenorrhea. In particular, symptoms should be consistent with the timing and characteristics of primary dysmenorrhea, and should not be severe or different from pain during previous menstrual cycles (see Table 2). Women with symptoms inconsistent with primary dysmenorrhea should be referred for medical evaluation of their symptoms. If symptoms are mild, aspirin or acetaminophen and/or local heat application may provide relief. However, NSAIDs are more effective for the treatment of primary dysmenorrhea.

NSAIDs

NSAIDs have several actions that can minimize dysmenorrhea symptoms. First, they inhibit the production of prostaglandins, which decreases uterine pressure and contractions. This improves blood flow to uterine tissue and reduces pain. In addition, by decreasing prostaglandins they decrease the associated symptoms which result from excess prostaglandins (e.g., nausea, vomiting, and headache).[7] NSAIDs also have a direct analgesic effect.

Pharmacokinetics

All three nonprescription NSAIDs mentioned above are rapidly absorbed and reach peak plasma concentrations in about one to two hours. Rapid absorption and onset of action are both beneficial characteristics in treating primary dysmenorrhea.

Efficacy

Clinical trials have shown that NSAIDs provide good symptom relief in most women with primary dysmenorrhea (66-90%).[3,8] Unfortunately, many women do not realize how effective NSAIDs are in managing primary dysmenorrhea. In one trial of adolescent girls, nearly 73% reported pain or discomfort with menstruation, but most of the girls had never taken a medication to relieve their symptoms.[9]

There are few comparative studies of the NSAIDs (both prescription and nonprescription products) used to treat primary dysmenorrhea.

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Yeast Infections

(Candida Vulvovaginitis)

A Focus on Nonprescription Drug Therapy

By Leslie Shimp, Pharm.D., M.S.
Associate Professor of Pharmacy, College of Pharmacy, University of Michigan
Consultant pharmacist, Department of Family Practice, Medical School, University of Michigan
This article was originally published in The RX Consultant*, Vol. V, No. 7, and is reprinted with permission.* *Copyright 1996 by Continuing Education Network, Inc.*

Learning Objectives: After reading this article, participants should be able to:

FOR YEAST INFECTIONS:
- Identify appropriate candidates for OTC therapy of vaginal yeast infections.
- Describe products available for OTC treatment of vaginal yeast infections.
- Distinguish vaginal yeast infections from bacterial yeast infections.

Overview

Yeast infection (Candida vulvovaginitis) is a common vaginal infection affecting significant numbers of women during their childbearing years. At least 75% of women experience one or more candida vaginal infections during their childbearing years, and 20-25% of all visits to physicians' offices for vaginitis are for candida vulvovaginitis.[1,2] The availability of nonprescription, over-the-counter (OTC) products for the treatment of candida vaginitis is changing the way these conditions are managed (see Table 1).

Compliance with Vaginal Antifungals is Essential

Despite the availability of effective therapy, many women with candida vaginitis remain inadequately treated. It has been suggested that chronic or recurrent candida infections are often due to noncompliance. A common barrier to compliance is lack of knowledge about the disease, available treatments, and the proper use of vaginal antifungal products.[3] This article reviews the symptoms of candida vulvovaginitis, describes who should—and who should not—self-treat, and outlines the appropriate use of OTC vaginal antifungals.

Candida Vulvovaginitis

Candida vulvovaginitis, commonly referred to as a yeast infection, is caused by the Candida fungi. These organisms are normally present in low numbers within the gastrointestinal tract or vagina of asymptomatic women, but infections occur when candida proliferates and invades vaginal tissue. About 85% of infections are caused by Candida albicans; the remainder are primarily caused by Candida tropicalis and Candida glabrata. The incidence of infections caused by C. tropicalis and C. glabrata has increased over the last two decades, and these species are more likely than C. albicans to be resistant to vaginal antifungal therapy.[4]

A number of risk factors for candida vaginitis have been studied.[1,5,6] Considerable controversy exists concerning the role of most of these factors in the development of candida infection (see Table 2).

Symptoms

Characteristic symptoms of candida vulvovaginitis include intense vulvar or vaginal itching, a thick, sometimes clumpy, whitish (cottage cheese-like) vaginal discharge, and vulvar erythema and/or irritation.[7] Most women experience itching or irritation, but only about 50% have the characteristic vaginal discharge. Other symptoms such as urinary frequency and external burning with urination are uncommon.[8] The feature that best distinguishes candida vulvovaginitis from other vaginal infections, such as bacterial vaginosis or trichomonas vaginitis, is the absence of an offensive odor from the vaginal discharge.

Treatment Overview

Self-treatment with a nonprescription antifungal product is most appropriate when: 1) a patient believes she may have candida vulvovaginitis based upon the similarity of current symptoms to those experienced during a previous clinician-diagnosed infection, 2) current symptoms are consistent with the characteristic symptoms of mild/moderate candida vulvovaginitis, particularly the absence of a foul-smelling vaginal discharge and significant urinary symptoms, and 3) vaginal symptoms are infrequent: no more than three candidal vaginal infections per year and none within the previous two months (see Table 3).

A small number of women, about 5% of the population, have chronic, recurrent infections. Recurrent candida vulvovaginitis is indicated by a return of symptoms within two months after treatment of a candidal vaginal infection, or four or more infections within 12 months.[9] Women who experience recurrent symptoms require further evaluation and should not self-treat. Chronic vaginal symptoms may indicate the presence of an undiagnosed medical condition (e.g., diabetes mellitus, HIV infection) or a resistant infection (a mixed infection

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TABLE 1

Nonprescription Drugs for the Treatment of Candida Vulvovaginitis

Vaginal antifungal drugs	Recommended regimen
Clotrimazole (Gyne-Lotrimin™, Mycelex-7™, others)	
100 mg vaginal tab	1 tab at bedtime for 7 days
1% vaginal cream	1 applicatorful at bedtime for 7 days
100 mg vaginal tab plus 1% vaginal cream	1 tab at bedtime for 7 days; apply topical cream to affected area twice daily (morning and evening) for 7 days
200 mg vaginal tab	1 tab at bedtime for 3 days
200 mg vaginal tab plus 1% vaginal cream	1 tab at bedtime for 3 days; apply topical cream to affected area twice daily (morning and evening) for 3 days
Miconazole (Monistat-7™, others)	
100 mg vaginal suppository (supp)	1 supp at bedtime for 7 days
2% vaginal cream	1 applicatorful at bedtime for 7 days
100 mg vaginal supp plus 2% vaginal cream	1 supp at bedtime for 7 days; apply topical cream to affected area twice daily (morning and evening) for 7 days
200 mg vaginal supp	1 supp at bedtime for 3 days
200 mg vaginal supp plus 2% vaginal cream	1 supp at bedtime for 3 days; apply topical cream to affected area twice daily (morning and evening) for 3 days
Butoconazole (Femstat-3™)	
2% vaginal cream	1 applicatorful at bedtime for 3 days
Ticonazole (Vagistat-1™)	
6.5% vaginal ointment	1 applicatorful at bedtime one time

Learning Objectives: After reading this article, participants should be able to:

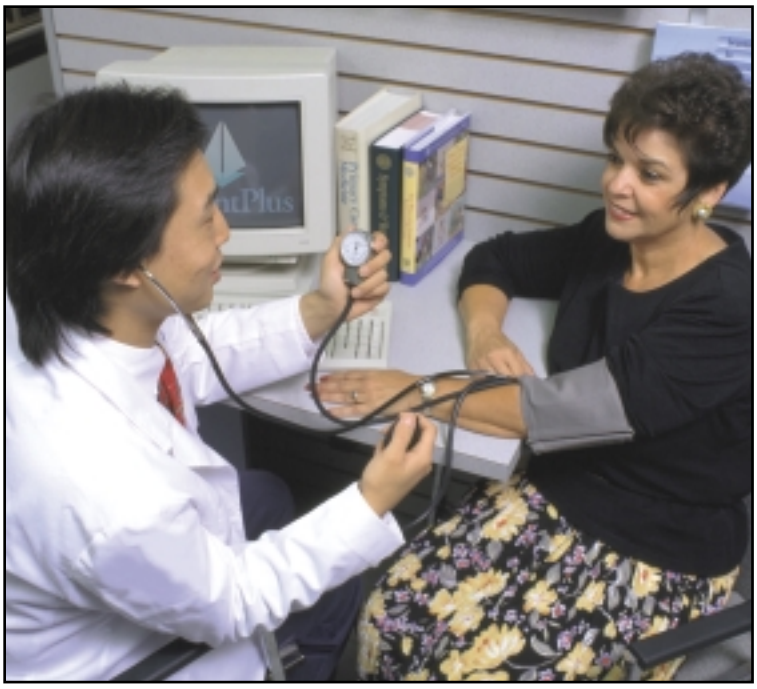
FOR CORONARY ARTERY DISEASE:

- Recognize the risk factors for coronary artery disease in women.
- Describe the symptoms most likely to present in women with coronary artery disease.
- Discuss the medical management of coronary artery disease in women.

Coronary Artery

Nearly 300,000 women in the U.S. die of coronary artery disease (CAD) each year, which is more than the number of women who die from all types of cancers combined. By the age of 60, 1 in 17 women in the U.S. has had a coronary event, compared with 1 in 5 men. After the age of 60, however, 1 in 4 women, as well as 1 in 4 men, die of CAD. Although the rates of mortality from CAD have been falling since the 1960s, the rate of decline has been slower among women than among men. Women with CAD experience more symptoms and are more likely to die as a result of their disease than men. A 50-year-old woman has about a 50% chance of developing CAD during her lifetime, and about a 30% chance of dying of CAD.

Fewer women than men have been enrolled in randomized trials investigating the treatment of CAD; however, this situation is improving.



Friendly Hills Pharmacy

Risk Factors for CAD

Coronary atherosclerosis is a disease of older women, and thus age is truly the greatest predictor of the development of CAD in women. Advanced age confers an increased risk of CAD in both women and men.

Other risk factors for CAD in women include smoking, diabetes, hypertension, family history of CAD, obesity, elevated cholesterol, and decreased estrogen levels (e.g., after menopause).

Individuals who smoke 25 or more cigarettes per day have a risk of CAD that is five times greater than that of nonsmokers. Even smoking 1-4 cigarettes per day doubles the risk of CAD. When women quit smoking, their risk of CAD starts to drop, and after 3-5 years, their risk approaches that of women who have never smoked. The effect of cigarette smoking is substantially greater among women who have other risk factors. Despite a general trend toward decreased smoking, the percentage of female teenagers who smoke has increased to approximately 25%. Smoking cessation reduces the risk of CAD more than any other change in CAD risk factors (see Table 1).

After smoking, diabetes is the next greatest contributor to CAD mortality in women; this association is more prevalent in women than in men. Mortality rates for CAD are 3-5 times higher among women with diabetes than among nondiabetic women, as compared with rates that are 2-4 times higher among men with diabetes than among nondiabetic men. Smoking, hypertension, and obesity act in synergy with diabetes to increase the risk of CAD. Smoking cessation and the control of high blood pressure and obesity yield greater reductions in the risk of myocardial infarction (MI)—heart attack—in patients with diabetes than in nondiabetic individuals.

Hypertension is another known and prevalent risk factor for CAD in both women and men. In women, the more severe the hypertension, the greater the risk of CAD. However, hypertensive women have a better prognosis than men, perhaps due to the benefits to the heart women receive from estrogen. Among men and women with the same blood pressure, women have a significantly lower risk of stroke, CAD, congestive heart failure, and sudden death. Women with a history of MI or stroke in their mother or a sibling before age 60 have a greater risk of CAD and MI than men with a similar history in their father.

The Framingham Study showed obesity to be an independent risk factor for CAD, especially for women. Truncal obesity (a waist to hip ratio greater than 0.8) was more important than the overall degree of obesity.

The presence of estrogen has significant positive effects on the lipid profile, raising HDL (good) cholesterol and lowering LDL (bad) cholesterol. Among women in particular, there is a significant inverse correlation between HDL levels and CAD, meaning the higher their HDL levels, the lower their risk of CAD. This female advantage diminishes gradually after menopause. However, most of the research on cholesterol and CAD has involved middle-aged men, and it is difficult to extrapolate these findings to women.

After Menopause

The incidence of CAD in women increases dramatically after menopause, which has led to the speculation that menopause marks the end of a protective effect from ovarian hormones. Indeed, women who had an early and abrupt menopause as a result of bilateral ovary removal and who did not receive estrogen replacement therapy (ERT) had a risk of CAD 2.2 times higher than that of premenopausal women of the same age. The combined results of over 30 studies on postmenopausal ERT and CAD have estimated that women who use hormone (estrogen and progestin) replacement therapy (HRT) have a 44% lower risk of CAD than nonusers. About one third of this effect is related to the positive effects of estrogen on cholesterol.

Estrogen has many other positive effects on the cardiovascular system which are also being investigated. These include possible interactions with the endothelium and smooth muscle in blood vessels and a possible role as an antioxidant. Studies have shown that the women who benefit most from ERT or HRT are women who already have CAD. A recent study using coronary angiograms demonstrated an increase in 10 years' survival from 60-97% in women with CAD who took HRT compared to women with CAD who did not take HRT. There is no evidence that the use of low

By Mary Beattie, M.D.
National Centers for Excellence in Women's Health
University of California, San Francisco, Medical Center
Assistant Professor of Medicine, University of California, San Francisco, School of Medicine

Disease in Women

dose oral contraceptives increases the risk of CAD among women under the age of 30 or among nonsmoking women who are 30 to 50 years old.

Clinical Presentation and Evaluation of CAD in Women

Women with CAD are more likely than men to experience angina (heart-related pain) as their first symptom. Angina in women is more likely to be associated with mental stress, sleep, and rest, as opposed to typical exertional angina. Fifty percent of men, compared with 34% of women, have a heart attack or MI as their first sign of CAD. Unfortunately, an initial MI is more likely to be fatal in women than in men (39% vs. 31%). There is also a higher proportion of silent MIs in women. Women who have an MI are less likely to show the classic electrocardiogram (EKG) criteria for MI (that is, to show a Q wave MI).

After an MI, women, especially black women, have a poorer prognosis. They are more likely to develop post MI angina or congestive heart failure, and they have a higher mortality rate than men. A recent study showed that 64% of women and 52% of black women, are alive four years after an MI, as compared to 79% of men. This may be due to other factors, such as differences in treatment, age, and diabetes. Men and women with diabetes have a poorer prognosis than nondiabetics. Compared with men, women with diabetes are twice as likely to die as a result of their MI. In one study of patients at the time of hospital discharge following an MI, 66% women with diabetes were alive compared with 87% of men with diabetes. After four years, these numbers dropped to 61% and 83% respectively.

Among diagnostic tools, the exercise treadmill test (ETT) has been used for decades to evaluate CAD in men and in some women, but only in recent years have studies been done to test its accuracy in women. The ETT has a high false positive rate in women (22-37% of positive results are falsely positive). The false negative rate is also high (estimated at 20-50%). When the resting EKG is abnormal and the history suggests angina, imaging with thallium or a newer radioisotope such as sestamibi can be done after exercise or stress testing to improve its accuracy.

Exercise or stress echocardiography is another noninvasive technique that can detect abnormalities in heart function in cases of myocardial ischemia. It has been reported to have a good predictive accuracy in single-vessel CAD, a common finding in women. This technique, however, requires an experienced echocardiographer, and there are concerns about its accuracy outside of university centers.

Invasive diagnostic testing with cardiac catheterization is done less frequently in women. Black women in particular—even those with histories similar to those of their white or male counterparts—are less likely to be referred for cardiac catheterization. Data from large registries suggest that women undergoing angiography have more total complications, arrhythmias, and hemorrhage. However, there is no difference in the incidence of death, MI, stroke, vascular complications, or contrast reactions between men and women.

Management Considerations

Medical management of CAD in women is similar to that in men, with the notable exception of HRT, which has been shown to significantly improve survival in women with CAD. HRT also has preventive effects for women with risk factors for CAD. HRT should be considered in all postmenopausal women who have CAD or who have significant risk factors for CAD. There is some evidence that nitrates are not as effective in reducing the frequency or intensity of anginal symptoms in women with chronic stable angina as they are in men. Women tend to have more symptoms of depression and fatigue with the routine use of beta blockers. Aspirin and beta blockers have comparable benefits in women and men for the prevention of reinfarction after MI. Aspirin probably also has preventive effects in women at risk for CAD, as it

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TABLE 1

Achievable Reduction in Risk for Various Interventions

Smoking Cessation	50-70%
Reduce serum cholesterol by 10%	25%
Decrease DBP 5 mm Hg	12%
Low-dose aspirin	33%
HRT	44%

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Breast Cancer

By Barbara Bolinger, Pharm.D.
Clinical Pharmacist, University of Southern California/ Kenneth Norris, Jr., Cancer Hospital and Research Institute
Assistant Professor of Clinical Pharmacy , University of Southern California School of Pharmacy

Christy Russell, M.D.
Associate Director, Breast Center, University of Southern California/Kenneth Norris, Jr., Cancer Hospital and Research Center
Assistant Professor of Medicine, University of Southern California School of Medicine

Learning Objectives: After reading this article, participants should be able to:

FOR BREAST CANCER:
- Identify which patients diagnosed with breast cancer are most likely to benefit from chemotherapy if given their clinical presentation.
- List the most common cytotoxic agents used in the adjuvant treatment of breast cancer.
- Compare and contrast the various therapeutic choices available for the treatment of breast cancer.

— Practice Pearls —

- Although risk factors help identify women who have a greater chance of developing breast cancer, women without risk factors are still at substantial risk and should receive regular, periodic screening.
- Hormone therapy (i.e., tamoxifen, megestrol, and anastrozole) appears to be most useful in postmenopausal women whose cancer is hormone receptor positive.
- The most common cytotoxic agents used in the adjuvant treatment of breast cancer are combinations of cyclophosphamide, methotrexate, 5-fluorouracil, and doxorubicin.
- Treatment of metastatic disease with paclitaxel, docetaxel, and vinorelbine has been shown to produce response rates in the range of 40-60% in patients with minimal or no prior chemotherapy.

In the United States, breast cancer is the most common cancer in women, accounting for nearly one-third of all their malignancies.[1] It is the second leading cause of cancer-related deaths for all American females, and the leading cause for women between the ages of 15 and 54. The scope and gravity of the problem are easily seen in the 1996 statistics for the US:

- Approximately 185,700 new cases of breast cancer were diagnosed that year, 99% of them in women.
- 44,560 deaths were attributed to the disease. [1]

Due to improved methods of detection, reports of breast cancer have increased steadily at 1-2% per year since 1960, but the mortality rate has remained stable for the last 50 years. This is due most likely to early intervention and improved methods of treatment. Because of the high incidence, even small improvements in the efficacy of treatment are important and may represent tens of thousands of lives saved every year.

As a result of the high failure rates that have been associated with therapies that treat the disease locally or regionally, there has been a concerted effort to find better treatments—or combinations of treatments—that would increase the cure rates of both primary and metastatic breast cancer.

This article will review current oncology recommendations, the status of adjuvant systemic therapies, and emerging factors that may significantly alter the future management of the disease. (The term adjuvant therapy refers to anticancer drugs or hormones given after surgery and/or radiation to help prevent recurrence of the cancer.)

Risk Factors

The causes of breast cancer are unknown, but some factors associated with its increased incidence are more widely accepted than others. For example, the risk becomes greater as individuals grow older. A family history of breast cancer is also an important risk factor, especially if the cancer occurred both in the mother and a sister and developed before menopause. Women who began menstruation at an early age, or entered menopause late in life, or never gave birth, or had a first pregnancy after age 30 are at higher risk. Although there is some controversy about the relationship between breast cancer and the use of birth control pills, evidence favors the position that women in general are not predisposed to the disease for this reason. The various groups mentioned above, however, may be at greater risk.

Screening and Diagnosis

There are three main screening methods used to detect breast cancer: breast self-examination (BSE), clinical physical examination, and imaging techniques—primarily mammography. About 90% of all palpable breast cancers are said to be detected by the patient, but the percentage detected by screening procedures such as mammography is increasing.

Current guidelines published by the American Cancer Society (see Table 1) recommend a monthly self-examination for women 20 and older. A breast examination by a physician should be performed at least every 3 years beginning at age 20, with an initial mammogram at age 40. For women with a family history of breast cancer, the first mammogram should be done at an earlier age. Annual mammograms and physical examinations are recommended for women 40 and older. Evidence indicates that early detection using these screening methods leads to a substantial reduction in mortality.

Most breast cancers are first discovered when a nodule is found during a physical examination or screening mammography.[2] The only proven way to determine whether either a palpable or nonpalpable breast lesion is cancerous is through tissue diagnosis by means of biopsy. Removing the tissue necessary for diagnosis by fine-needle aspiration is less invasive than excisional biopsy, and this has now become the routine procedure preferred by many surgeons.[1]

After the diagnosis of breast cancer is made, the treatment options include surgical procedures such as segmental resection or modified radical mastectomy, radiotherapy, hormone therapy, and chemotherapy.

Staging

The staging process assesses prognostic factors and the presence of metastases and aids in the selection of postsurgical therapy. The number of microscopic malignant nodes out of the total number of nodes sampled is the single most predictable indicator of long-term prognosis. The routine use of serum tumor markers, however, has not yet been shown to be of value in breast cancer prognosis.[3]

The clinical staging system of the International Union Against Cancer (UICC) is based on the TNM (tumor, nodes, metastases) system (see Tables 2 and 3)[2] and has now gained universal acceptance.

Prognosis

There are a number of tumor characteristics that may be prognostic factors for stage I or stage II breast cancer. One of the most common characteristics that affects the risk of recurrence, regardless of initial node status, is estrogen receptor (ER) content. The ER content of a specimen is evaluated at the time of tumor removal. In general, patients with ER-positive and/or PR (progesterone receptor)-positive tumors seem to have a better prognosis, even if advanced disease is present.

Survival rates in patients with metastatic disease vary with the location and type of metastases. Women with osseous (bone) and cutaneous (skin) metastases may survive for several years, whereas those with lymphangitic metastases of the lung and/or extensive liver metastases have a mean survival duration of only three to six months.[3]

Therapeutic Choices

The treatment of breast cancer has changed somewhat over the last two decades, but very little progress has been made. The surgical treatment of the disease in its early stage consists of either total or partial mastectomy (lumpectomy), with an associated lymph node dissection. Partial mastectomy is usually followed by radiation therapy to prevent local recurrence. Whenever possible, partial mastectomy is chosen to conserve breast tissue.

Adjuvant systemic therapies, whether hormonal or cytotoxic, have become part of the standard treatment for primary breast cancer. Studies of these therapies generally report the percentage of women with a positive response (where response is defined as tumor shrinkage or lack of disease progression). Results of systemic therapies were summarized and issued as a series of recommendations (see Table 4)[4] based on the Fourth International Conference on Adjuvant Therapy of Primary Breast Cancer. These recommendations indicate that adjuvant tamoxifen therapy may be more effective in women over the age of 50, while adjuvant cytotoxic therapy has its greatest impact on younger women.

TABLE 1

American Cancer Society Screening Recommendations

Breast Self Exam (BSE)	20 years and older	Monthly
Clinical Physical Exam	20 - 40 years 40 and over	Every 3 years Every year
Mammography	40 years of age	Baseline and yearly

TABLE 2

Definitions for Breast Cancer Staging[5]

Tumor

TIS	Carcinoma in situ (intraductal carcinoma, lobular)
T0	No evidence of primary tumor
T1	Tumor 2 cm in greatest dimension
T2	Tumor >2cm but <5cm in greatest dimension
T3	Tumor >5cm in greatest dimension
T4	Tumor of any size with direct extension into chest wall or skin

Nodes

N0	No regional lymph node metastases
N1	Metastases to movable ipsilateral axillary node(s)
N2	Metastases to ipsilateral axillary lymph node(s), fixed to one another or other structures

Metastases

M0	No distant metastases
M1	Metastases to movable ipsilateral axillary node(s), metastases to ipsilateral axillary lymph node(s), fixed to one another or other structures, or metastases to ipsilateral internal mammary lymph node(s); distant metastases.

TABLE 3

Classification of Breast Cancer Stages[5]

Stage 0:	T1S, N0, M0
Stage I:	T1, N0, M0
Stage IIA:	T0, N1, M0
Stage IIB:	T2, N1, M0 or T3, N0, M0
Stage IIIA:	T0, N2, M0 or T1, N2, M0 or T2, N2, M0 or T3, N1 or N2, M0
Stage IIIB:	T4, any N, M0 or any T, N3
Stage IV:	Any T, any N, M1

TABLE 4

Recommendations on Adjuvant Therapy of Primary Breast Cancer[4]

GROUP	ADJUVANT THERAPY
PATIENTS WITH NODE-NEGATIVE TUMORS	
Low risk of recurrence	
Premenopausal	None or tamoxifen
Postmenopausal	None or tamoxifen
Elderly	None
Intermediate risk of recurrence	
Postmenopausal	Tamoxifen
Elderly*	Tamoxifen
High risk of recurrence	
Premenopausal, hormone-receptor positive	Chemotherapy, with or without tamoxifen
Premenopausal, hormone-receptor negative	Chemotherapy
Postmenopausal, hormone-receptor positive	Tamoxifen, with or without chemotherapy
Postmenopausal, hormone-receptor negative	Chemotherapy, with or without tamoxifen
Elderly	Tamoxifen (chemotherapy in selected cases)
PATIENTS WITH NODE-POSITIVE TUMORS	
Premenopausal, hormone-receptor positive	Chemotherapy, with or without tamoxifen
Premenopausal, hormone-receptor negative	Chemotherapy
Postmenopausal, hormone-receptor positive	Tamoxifen, with or without chemotherapy
Postmenopausal, hormone-receptor negative	Chemotherapy, with or without tamoxifen
Elderly, hormone-receptor positive	Tamoxifen
Elderly, hormone-receptor negative	Chemotherapy (if tolerated), with or without tamoxifen

* >70 years of age

TABLE 5

Hormonal Therapy

CLASS	DRUG	DOSE	SIDE EFFECTS
Antiestrogen	Tamoxifen	20 mg daily	Weight gain, vaginal bleeding, hot flashes, DVT, nausea, and vomiting
Progestin	Megestrol	40 mg 4 times daily	Fluid retention, weight gain, and hot flashes
LHRH Agonists	Leuprolide	3.75 mg IM Depot	Edema, pain, hot flashes, and asthenia
	Goserelin	3.6 mg IM Depot	Hypercalcemia, vaginal bleeding, hot flashes, pain, and lethargy
Aromatase Inhibitor	Anastrozole	1 mg daily	Asthenia, nausea, headache, hot flashes, and back pain

Hormonal Therapy

The use of hormone therapy has increased since more sophisticated hormone-receptor assays have become available, and new types of treatments have been introduced. The therapies of the past, such as major surgery, have given way in many cases to treatment with antiestrogens, progestins, and aromatase inhibitors (see Table 5). Choosing which hormonal therapy is best for a particular patient depends on the patient's response and tolerance of side effects.

The antiestrogen tamoxifen has been shown to delay tumor recurrence and prolong the survival of postmenopausal women. Tamoxifen blocks the release of two potent factors, growth factor beta and the insulin-like growth factor I (IGF-1), which slows tumor growth.[3] Tamoxifen is also effective as adjuvant therapy in premenopausal women with breast cancer that is ER-positive.

The standard therapeutic dose of tamoxifen is 20 mg/day orally, and should be continued for a minimum of two years or until the disease progresses. Toxicity from tamoxifen is usually mild and transient, with the most common side effects being weight gain, vaginal bleeding (endometrial hyperplasia), skin rash, hot flashes, deep vein thrombosis, thrombocytopenia, hypercalcemia, nausea, vomiting, and the progression of cataracts.

Another hormonal therapy that is available is the semisynthetic progestin megestrol acetate. The commonly used therapeutic dosage is 160 mg/day in divided oral doses. Randomized trials have confirmed that for patients who have not had prior endocrine therapy, megestrol acetate is therapeutically equivalent to tamoxifen. However, the response rate is low (<10%) if megestrol acetate is used after two or three other hormone treatments.[5] Toxicity with this therapy is also mild and transient, and side effects include fluid retention, weight gain, and hot flashes.

Leutinizing hormone-releasing hormone (LHRH) agonists such as leuprolide and goserelin decrease follicle stimulating hormone and leutinizing hormone excretion and may have a direct effect on breast cancer. The LHRH agonists are effective in premenopausal women with metastatic disease. They are easy to administer as a once monthly depot injection and have minimal toxicity.

The newest addition to the hormone therapy family is the aromatase inhibitor anastrozole. It is indicated for use in postmenopausal women whose disease has progressed following tamoxifen therapy. The recommended dose is 1 mg taken orally once a day.

Patients with estrogen-receptor negative disease that doesn't respond to tamoxifen probably will not respond to anastrozole therapy either. When compared to treatment with megestrol acetate, more than 60% of patients responded for longer

than six months when given anastrozole, and more than 15% responded for longer than 12 months. There was no difference in efficacy between the two treatments.[6] The most commonly reported side effects included weakness (16%), nausea (15%), headache (13%), hot flashes (12%), and bone or joint pain (10.7%). Diarrhea was more common with anastrozole than with megestrol acetate.

First-Line Chemotherapy

Cytotoxic chemotherapy is the treatment of choice for patients who have hormone refractory tumors or whose tumors become hormone-resistant.[7] The cytotoxic agents most commonly used in the adjuvant treatment of breast cancer are cyclophosphamide (C), methotrexate (M), 5-fluorouracil (F), and doxorubicin (A) used in combination (see Table 6).[5] These combinations are associated with therapeutic response rates of 50-70%. Regimens that include doxorubicin have been shown to produce higher overall and complete response rates and longer durations of response and survival.

A reasonable approach to determining which combination of agents is best suited to a particular patient is to use CMF combinations for low-risk patients (those with good prognostic factors), and FAC or AC with higher risk groups.[8]

The adverse effects of chemotherapy regimens are still a major concern. Table 7 summarizes the early toxic effects and the average frequency for the two most common chemotherapeutic regimens.[5] Significant hair loss occurs in fewer than 10% of patients, but is to be expected when a doxorubicin-based regimen is employed.

Approximately one-third of patients complain of anticipatory nausea and/or vomiting. Weight gain during adjuvant chemotherapy has been consistently documented in at least half of the women receiving this therapy, with an average weight gain of 3-4 kg. Major delayed toxic effects include irreversible amenorrhea (<40 years: 40%; >40 years: 95%). Doxorubicin-based treatments have a 1-2% incidence of congestive heart failure if the cumulative lifetime dose does not exceed 300-350 mg/m^2. The risk of heart failure increases dramatically if this dose is exceeded.

Second-Line Chemotherapy

When first-line chemotherapy becomes ineffective and metastatic disease progresses, second-line agents are employed. These are either single-agent therapies or combinations not previously used. The new combinations may include vinca alkaloids (vincristine, vinblastine), mitomycin, mitoxantrone, etoposide, cisplatin, carboplatin, and thiotepa.

The response rate from the use of this type of combination therapy usually approaches 20-25%, and this type therapy usually remains effective for a shorter time. New agents such as taxanes, the new vinca alkaloid vinorelbine, and topoisomerase inhibitors, which prevent tumor growth through a different mechanism than older drugs, have provided a much-needed boost to the chemotherapeutic armamentarium (see Table 8).

Paclitaxel, a taxane that disrupts microtubules and cell division, is one of the newest single-agent chemotherapeutic options available for refractory disease. The response rate in patients with minimal prior chemotherapy is well above 50%, but a decrease in that response rate has been noted depending on the amount of previous chemotherapy the patient has undergone. Patients in the latter category still show a 23% response rate, even where there is doxorubicin resistance.[9]

Paclitaxel doses ranging from 135-250 mg/m^2 have been used and infused over three hours. All patients should be premedicated before pacilaxtel is administered to prevent severe hypersensitivity reactions. The manufacturer recommends dexamethasone (IV or PO), IV diphenhydramine and IV cimetidine 30-60 minutes prior to administration. Neither optimal dosage and treatment schedules nor combination therapies have been defined.

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TABLE 6

Effective Combination Chemotherapy Regimens Commonly Used to Treat Breast Cancer[5]

Regimen	Dose (mg/m^2)	Route	Day(s) of Treatment	Recycle
CMF (P)				
Cyclophosphamide	100	PO	1 to 14	
Methotrexate	40 (60)	I.V.	1 and 8	4 wks
Fluorouracil	600 (700)	I.V.	1 and 8	
Prednisone	(40)	(PO)	(1 to 14)	
CMF				
Cyclophosphamide	600	I.V.	1	
Methotrexate	40	I.V.	1	3 wks
Fluorouracil	600	I.V.	1	
CMF				
Cyclophosphamide	600	I.V.	1 and 8	
Methotrexate	40	I.V.	1 and 8	4 wks
Fluorouracil	600	I.V.	1 and 8	
CA				
Cyclophosphamide	200	PO	3 to 6	3-4 wks
Doxorubicin	40	I.V.	1	
AC				
Doxorubicin	45	I.V.	1	3 wks
Cyclophosphamide	500	I.V.	1	
FAC				
Fluorouracil	500	I.V.	1 and 8	
Doxorubicin	50	I.V.	1	4 wks
Cyclophosphamide	500	I.V.	1	

TABLE 7

Acute and Late Toxicity From Commonly Used Adjuvant Chemotherapy Combinations[5]

Toxicity	CMF (%)	FAC or AC (%)
Acute Vomiting	>90	>90
Oral Mucositis	<10	
Marked Alopecia	10	>90
Leukopenia*	10	25
Thrombocytopenia	<10	<5
Conjunctivitis	30	
Cystitis	15	<5
Delayed Amenorrhea	70	80
Congestive Heart Failure	0	1-2
Late Acute Leukemia	<1	<1

*<2500/mm3
<75,000/mm3

(Data are averages derived from the published literature)

EPITHELIAL

Ovarian Cancer

Leanne M. Sakamoto, Pharm.D.
Clinical Pharmacist, University of Southern California/Kenneth Norris, Jr., Cancer Hospital and Research Institute
Assistant Professor of Clinical Pharmacy, University of Southern California School of Pharmacy

Practice Pearls

- Ovarian cancer is the 4th leading cause of cancer deaths in the United States.
- Early detection of ovarian cancer is crucial for improving the overall prognosis.
- The combination of platinum compounds with paclitaxel is considered the optimal first-line chemotherapy.
- Patients receiving cisplatin must be adequately pre-hydrated and pre-treated with antiemetics.
- Topotecan is a new chemotherapeutic agent approved for treatment of advanced ovarian cancer in patients who have failed first-line or subsequent therapy.

Learning Objectives: After reading this article, participants should be able to:

EPITHELIAL OVARIAN CANCER:

- State the survival rates associated with the diagnosis and treatment of ovarian cancer at early and advanced stages.
- List at least six risk factors for the development of ovarian cancer.
- Identify and describe the treatments used for ovarian cancer, differentiating between those that are considered first line, those used for persistent or recurrent disease, and those that are considered palliative in nature.

Introduction

Ovarian cancer is the fourth leading cause of cancer deaths in women and is the leading cause of gynecological cancer death in the United States. It affects primarily postmenopausal women in their sixth decade. In the United States, it is estimated that approximately 26,700 new cases of ovarian cancer were diagnosed, and an estimated 14,800 deaths were associated with ovarian cancer in 1996.[1,2] Clearly, the social and economic impact of ovarian cancer is enormous.

Ovarian cancer, when diagnosed and treated in its early stage, has a 5-year survival rate of 91%.[1] Unfortunately, because ovarian cancer in its early stage is often silent, 60-70% of patients will have advanced disease at the time of diagnosis—a point at which the tumor has spread to the peritoneal surfaces of the upper abdomen. The prognosis for these women is poor because it is difficult to eradicate extensive intra-abdominal disease by surgical debulking, and many patients will have only a partial response to chemotherapy. The 5-year survival rate for advanced disease is only 23%.[1]

There are three major types of ovarian cancer: epithelial, germ cell, and stromal. Of the three, epithelial ovarian cancer is the most common. Epithelial ovarian tumors account for 80-90% of all cases. This article focuses on epithelial ovarian cancer, its risk factors, diagnosis, screening and treatment, with an emphasis on chemotherapeutic options.

Risk Factors

The exact cause of ovarian cancer is unknown; however, risk factors have been identified. Awareness of these risk factors may help provide for timely screening for ovarian cancer (see Table 1).

Age

The risk of ovarian cancer increases with age. Ovarian cancer usually develops in women more than 40 years of age. The peak incidence is in women between the ages of 55 and 59 years. Postmenopausal women are at greater risk.

Nulliparity and Ovulation

Never having borne a child (nulliparity), pregnancy after the age of 35, few pregnancies, and late menopause all increase the risk for ovarian cancer. Ovarian cancer is thought to be linked to many years of constant ovulation, which makes malignant transformation of the ovarian epithelium more likely. Each pregnancy reduces the risk of ovarian cancer by 10%. The use of oral contraceptives, which suppress ovulation, has also been shown to decrease the risk of ovarian cancer.

Genetic Factors

Lately, the study of genes linked to cancer has been widely publicized. Three hereditary syndromes have been identified which carry an increased risk of ovarian cancer: site-specific ovarian cancer, hereditary breast-ovarian cancer syndrome, and Lynch syndrome II. Hereditary breast-ovarian cancer syndrome is the most common. It is associated with mutations of the breast cancer genes (BRCA1 and BRCA2). Women with this condition have a greater than 90% risk of developing breast or ovarian cancer by the age of 70.[3]

Screening

Because ovarian cancer in its early stages has a much better prognosis than late disease, there is a need for early diagnosis. Unfortunately, detecting ovarian cancer early is difficult. There is no one proven screening method which allows for early detection and provides improved survival. Currently, the American Cancer Society recommends that all women over the age of 40 have a cancer-related checkup yearly which includes a pelvic examination to aid in the early detection of ovarian cancer.[1]

TABLE 1

Risk Factors for Ovarian Cancer

Positive Risk Factors

Women > 40 years old

Nulliparity or 1st pregnancy after the age of 35

Hereditary conditions (e.g., Hereditary breast-ovarian cancer syndrome)
Negative Risk Factors

Oral contraceptives

Pregnancy (each pregnancy reduces the risk of ovarian cancer by 10%)

TABLE 2

Staging of Ovarian Cancer[3]

International Federation of Gynecology and Obstetrics (FIGO) staging of ovarian cancer

Stage I: Disease limited to ovaries

- IA: tumor limited to one ovary; tumor capsule intact; no tumor on ovarian surface
- IB: disease in both ovaries; tumor capsule intact; no tumor on ovarian surface
- IC: tumor limited to one or both ovaries with any of the following:
  - capsule rupture
  - tumor on ovarian surface
  - malignant cells in ascites or peritoneal washings

Stage II: Disease involves one or both ovaries with pelvic cavity spread

- IIA: malignancy extending or metastasizing into the uterus or fallopian tubes
- IIB: tumor extending into other pelvic tissues
- IIC: tumor is either stage IIA or IIB with malignant cells in ascites or peritoneal washings

Stage III: Disease found in one or both ovaries with peritoneal metastasis outside the pelvis and/or regional lymph node spread

- IIIA: microscopic peritoneal metastasis beyond pelvis
- IIIB: macroscopic peritoneal metastasis beyond pelvis <20 mm in diameter
- IIIC: peritoneal metastasis beyond pelvis >20 mm in diameter and/or regional lymph node metastasis

Stage IV: Tumor involving one or both ovaries with distant metastases or liver metastasis or positive pleural effusion

A thorough, annual pelvic exam is an important means of identifying pelvic masses. However, this exam may not be sensitive enough or specific enough to adequately screen for ovarian cancer. Often masses can be missed, and not all masses that are detected are malignant. All women, particularly perimenopausal and postmenopausal women with abdominal or pelvic symptoms, should have a thorough physical and pelvic exam as part of their work-up. The most common symptom of ovarian cancer is vague gastrointestinal discomfort, such as bloating, fullness and early satiety, pelvic pressure and pain. If a mass is detected, further diagnostic tests are warranted. However, a definitive diagnosis of ovarian cancer is usually established by tumor biopsy at the time of an exploratory laparotomy, when staging of the cancer and tumor debulking also take place.

Women who are at high risk for ovarian cancer may benefit from additional screening by transvaginal ultrasound and CA-125 serum tumor marker studies.[4] These two methods also can aid in determining if a detected mass requires surgical evaluation. Transvaginal ultrasonography is a useful method for imaging the ovary. It provides information that is predictive of the presence of cancer. However, this method also lacks specificity. In a study of 5,479 women, based on the findings of transvaginal ultrasound, only one case of ovarian cancer was found for every 65 exploratory laparotomies performed.[4]

The CA-125 antigen is a serum tumor marker that is elevated in 80% of epithelial ovarian cancers. However, because elevated levels are only present in 50% of patients with early-stage ovarian cancer, the risk for false negatives is substantial. In addition, premenopausal women may have nonmalignant conditions, including endometriosis, pregnancy, and benign cysts that can raise CA-125 levels above normal, causing false positive results. Because of this, CA-125 is not an adequate screening test to be used alone, although it can be very useful in monitoring for early recurrence of disease.[4]

Diagnosis and Staging

Since benign ovarian masses are indistinguishable from malignant masses by ultrasound and many benign conditions can cause an elevated CA-125 level, an exploratory laparotomy is often necessary to diagnose ovarian cancer. If ovarian cancer is confirmed, a surgical resection or debulking of as much ovarian cancer as possible, as well as a total abdominal hysterectomy, a bilateral salpingo-oophorectomy (removal of the ovaries and fallopian tubes), and an omentectomy (removal of the omentum; a fold of peritoneum) are usually performed. In addition, biopsies of lymph nodes and other suspected areas are performed, and a sample of fluid from ascites (if present) is checked for malignant cells to aid in the staging and grading of the cancer.

TABLE 3

Initial Chemotherapeutic Regimens Commonly Used to Treat Ovarian Cancer

Agents	Dose/Schedule	Cycle	Response Rate
Cyclophosphamide Cisplatin	750 mg/m^2 IV 75 mg/m^2 IV	every 21 days for 6 cycles	Overall response rate 60% median survival 24 months[8]
Cyclophosphamide Carboplatin	600 mg/m^2 IV 300 mg/m^2 IV	every 28 days for 6 cycles	Similar to above with less toxicities
Paclitaxel Cisplatin	135 mg/m^2 IV 75 mg/m^2 IV	every 21 days for 6 cycles	Overall response rate 73% median survival 38 months8
Paclitaxel Carboplatin	135-175 mg/m2 IV Dose calculation using Calvert Formula with an AUC of 5-7*	every 21 days for 6 cycles	Similar to above with less toxicities.

* Carboplatin dose calculation using Calvert Formula: Carboplatin total dose (mg) = target AUC X (GFR + 25) target AUC ranges from 5-7
GFR = patients calculated creatinine clearance

TABLE 4

Chemotherapeutic Agents for Ovarian Cancer

Drug	Dose	Side Effects	Special Considerations
Cisplatin (Platinol™)	50-75 mg/m^2 IV every 3 weeks	Highly emetogenic (acute and delayed emesis), nephrotoxicity, ototoxicity, neurotoxicity	Nephrotoxicity reduced with mannitol and pre-hydration. Neurotoxicity can be additive with paclitaxel. Pre-treat with antiemetic HT-3 receptor antagonist (granisetron or ondansetron).
Carboplatin (Paraplatin™)	400-500 mg/m^2 IV every 3 weeks	Myleosuppression, dose-limiting thrombocytopenia, nausea and vomiting	Efficacy equal to cisplatin. Lower emetogenic potential than cisplatin. Pre-hydration not necessary. Platelet nadir occurs 3 weeks post treatment with recovery at 4-5 weeks. Calvert Formula*: target AUC X (GFR + 25) = total dose (mg)
Cyclophosphamide (Cytoxan™)	500-1500 mg/m^2 IV every 3 weeks	myleosuppresion, dose-limiting leukopenia, hemorrhagic cystitis, alopecia	Hemorrhagic cystitis can be reduced with adequate hydration. Leucocyte nadir occurs 8-14 days post treatment with recovery at 18-25 days.
Paclitaxel (Taxol™)	135-175 mg/m^2 IV every 3 weeks	Myleosuppresion, dose-limiting leukopenia, dose-limiting peripheral neuropathy, cardiotoxicity, alopecia	Pre-treat with dexamethasone, diphenhydramine and cimetidine or ranitidine to prevent hypersensitivity reactions. Active against platinum-resistant tumors. Leukocyte nadirs occur 10 days after treatment with recovery at 15 days. Prepared paclitaxel for IV infusion should be in glass or non-PVC containers. Non-PVC nitroglycerin tubing should be used for administration with a 0.2 m in-line filter.
Topotecan (Hycamtin™)	1.5 mg/m^2 IV daily for 5 days, repeat every 21 days	Myleosuppression, dose-limiting neutropenia, nausea/vomiting, alopecia	Treatment should be held if ANC < 1500 cells/mm^3. Neutrophil nadir occurs at 11 days with recovery at 18 days. Antiemetics are not routinely necessary. If G-CSF is necessary it should not be given until day 6 to prevent prolongation of neutropenia.

* Calvert Formula calculates carboplatin dose based on patient's creatinine clearance (GFR). Target AUC of 5-6 is generally used for combination chemotherapy.

Staging of the cancer is based on the extent and location of disease found at the time of surgery (see Table 2). The prognosis of ovarian cancer depends on the stage and tumor grade at the time of surgery—the higher the stage and grade of the cancer, the poorer the prognosis. The presence of residual disease after initial surgery also influences the prognosis.

First-Line Treatment

Surgery is the primary treatment for ovarian cancer, which allows for accurate staging, diagnosis, and optimal debulking. The stage and grade of the tumor determine the need for chemotherapy after surgery. Following surgery, patients with stage IA tumors and most patients with stage IB tumors (which are well differentiated) do not require chemotherapy.[4] These patients have a 5-year disease-free survival of 91-98%, which is not improved by chemotherapy.[7] Unfortunately, only 25% of women with newly diagnosed ovarian cancer will have stage I disease at the time of diagnosis. As mentioned earlier, the majority of women will have advanced disease at the time of diagnosis. Despite treatment with platinum-based chemotherapy, the overall survival rate for advanced disease (stage III or IV) is only 10-30%.[7]

The combination of platinum drugs—carboplatin (Paraplatin™) or cisplatin (Platinol™)—with paclitaxel (Taxol™) is considered first-line initial chemotherapy for treatment of advanced disease following surgery (see Table 4).[4] Studies have shown that this combination improves the duration of progression-free survival and overall survival in women with advanced stage ovarian cancer when compared to platinum drugs combined with cyclophosphamide (Cytoxan™).[4,7,8]

A study of 410 women with advanced ovarian cancer with residual masses larger than 1 cm after initial surgery demonstrated that cisplatin with paclitaxel resulted in a 73% response. (By contrast, cisplatin with cyclophosphamide resulted in a 60% response.)

Progression-free survival was also significantly longer in the cisplatin-paclitaxel group than in the cisplatin-cyclophosphamide group; 18 vs. 13 months respectively. Overall survival was also significantly longer in the cisplatin-paclitaxel group than in the cisplatin-cyclophosphamide group.[8] Because of results from similar studies, platinum-paclitaxel combinations have replaced platinum-cyclophosphamide as first-line therapy.

Although cisplatin has good activity in advanced ovarian cancer, toxicity can be a problem. Cisplatin causes nausea and vomiting in almost all patients and can cause nephrotoxicity as well as neurotoxicity. When combined with paclitaxel, the neurotoxic effects can be additive. Carboplatin, an analogue of cisplatin, has been shown to have efficacy equal to cisplatin when used in combination with cyclophosphamide and paclitaxel, but with fewer toxicities.[4,7,9] Carboplatin causes less nausea, vomiting and neurotoxicity and is better tolerated than cisplatin. In addition, carboplatin can be considered easier to administer because pre-hydration is not necessary. Consequently, many physicians are using carboplatin plus paclitaxel as first-line treatment for ovarian cancer (see Table 3).

Recently, a new medication called amifostine (Ethyol™) was approved by the FDA for use in reducing cumulative renal effects associated with repeated use of cisplatin in patients with advanced ovarian cancer and nonsmall-cell lung cancer. Amifostine, when given prior to cisplatin, reduces the renal toxicities of cisplatin while having no effect on cisplatin's antitumor activity. Amifostine is initiated, 30 minutes prior to the start of chemotherapy, with a dose of 910 mg/m^2 IV given over 15 minutes. The most common side effects are hypotension, nausea and vomiting. Patients receiving amifostine should receive pretreatment with an antiemetic, such as granisetron or ondansetron, and 20 mg of dexamethasone IV. The manufacturer of amifostine recommends hydration prior to infusing amifostine and infusing the medication while the patient is lying down to decrease the drug's hypotensive effects.

Treatment for Persistent or Recurrent Disease

Although most women with advanced disease respond to first-line treatment, they still have a 40-50% chance of relapse within two years following initial treatment.[6] Unfortunately, most patients eventually die of progressive disease that is resistant to available chemotherapeutic agents. Women who relapse after primary chemotherapy with platinum can be divided into two groups based on their interval to relapse. Women who relapse six months after treatment can be successfully retreated with subsequent platinum-containing regimens. Those who relapse earlier, within six months of treatment, have a poor subsequent response to platinum-containing regimens. This group of patients may benefit from paclitaxel, which has a response rate of 35%.[4] However, with the increasing use of paclitaxel as a first-line agent and the occurrence of resistance, there is a need for the development of new agents which can be used as second-line therapy for recurrent disease. **Recently, several new chemotherapeutic agents were approved by the FDA. These include topotecan (Hycamtin™), gemcitabine (Gemzar™), liposomal doxorubicin (Doxil™), and docetaxol (Taxotere™). Of these, topotecan (Hycamtin™) is the only one approved for second-line or subsequent therapy in women with advanced ovarian cancer.**

Topotecan is a topoisomerase I inhibitor. It is an analog of camptothecin, a plant alkaloid derived from the oriental tree Camptotheca acuminata. It is FDA approved for the treatment of patients with metastatic ovarian cancer after failure of initial or subsequent chemotherapy. Topotecan's FDA approval was based, in part, on data from an open, randomized comparative study of women who had failed one prior platinum-based chemotherapy regimen and who had no prior paclitaxel treatment. This study compared topotecan with paclitaxel. Patients treated with topotecan had a significantly longer progression-free survival (23 vs. 14 weeks) and higher response rates (20% vs. 13%) when compared to patients who received paclitaxel.[10] Additional studies have reported response rates of 4-28% in previously platinum treated patients, including platinum-resistant patients.[11] These studies indicate that topotecan is an effective second-line agent in patients who fail platinum and paclitaxel. Topotecan is given as a dose of 1.5 mg/m^2 by IV infusion over 30 minutes for 5 consecutive days every 21 days, with treatment for at least four courses. No dosage adjustments are necessary for patients with hepatic impairment; however, patients with moderate renal impairment (Ccr 20-39 ml/min) should receive a reduced dose of 0.75 mg/m^2. The dose-limiting toxicity of topotecan is bone marrow suppression, particularly neutropenia (an abnormally small number of white blood cells). Severe neutropenia (<500 cells/mm^3) occurs in 80% of patients with a nadir occurring at day 11. The median duration of neutropenia is about seven days. Severe thrombocytopenia (an abnormally small number of platelets) and anemia can also occur. Topotecan

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Depression

Martha Pauli, M.Ed., Pharm.D.
Drug Education Coordinator, Kaiser Permanente

— Profiles —

– 1 –

Linda, 48, comes into the pharmacy to pick up her prescription for an antidepressant. She says her family is not supportive of her taking this medicine. They think she takes too much, and have called it an upper, a crutch, and addicting. She's trying to take it only when she needs it. She asks, "Shouldn't I feel better right away after I take it?"

Learning Objectives: After reading this article, participants should be able to:

FOR WOMAN AND DEPRESSION:
- Distinguish the advantages and disadvantages of each type of antidepressant.
- Describe three factors to consider when using antidepressants in women.

– 2 –

Joan, 33, comes in to ask your opinion of using St. John's wort to treat her lack of energy and depressive symptoms. She was previously treated with paroxetine (Paxil™) and felt it helped her depression, but libido difficulties forced her to stop taking it.

– 3 –

Mary, 28, a mother of three, including a new infant, wonders about taking a medicine for depression while breast-feeding. She feels she has no energy, cries a lot, feels overwhelmed, and has a hard time caring for the children.

– 4 –

Susan, 35, has been on prescription diet pills in the past. She comes to the pharmacy with a prescription for fluoxetine (Prozac™) from another doctor. She heard this is one antidepressant that doesn't cause weight gain, and she is eager to try it for that reason.

– 5 –

Jane, 70, relates that she has many physical complaints, has low energy and just can't seem to concentrate. "I guess that is just what happens with getting older," she says.

What do all these women have in common? They may be experiencing symptoms of depression—an all too common, but treatable illness.

Frequency and Cost of Depression

Millions of adults suffer from depression; it is more common than coronary heart disease or cancer. More women than men are affected, with the ratio of women to men approaching 2:1. Depression is underdiagnosed and undertreated in the primary care setting. A recent consensus statement in the Journal of the American Medical Association concluded that even though safe, effective, and affordable treatments are available, barriers to treatment remain within the medical community and the general public, leading to under-recognition and undertreatment of this condition (see Table 1).

The costs of depression are staggering. Direct costs include treatment with antidepressant drugs, other auxiliary medications, other therapies (e.g., psychotherapy), and increased use of medical services in general. Indirect costs include absence from work and lost productivity, social, physical, and family disabilities, and mortality costs (i.e., suicide). Estimates have placed the total cost of depression at approximately $44 billion a year in the United States.

The Pharmacist's Role in the Treatment of Depression

Pharmacists, as patient advocates, can have a positive impact on a patient's quality of life by monitoring and supporting rational antidepressant drug treatment. Knowledge of the diagnostic criteria for depression and the medical illnesses and drugs that may contribute to depression is important (see Tables 2 and 3).

What should pharmacists consider when responding to the women in the cases described above?

Profile 1: Depression is not caused by a personal weakness or lack of willpower. Antidepressants are not addicting or habit-forming, nor are they uppers in the abusive sense of the word. In fact, depression is one of the most treatable—medication responsive—of all mental illnesses. It usually takes from 4-6 weeks for a full therapeutic trial, although some symptoms begin to resolve sooner (see Table 4).

Profile 2: Various alternative or folk medications are promoted in current magazines and literature. One German medicinal is St. John's wort. This compound is an extract from the plant Hypericum perforatum and appears more effective

TABLE 1

Barriers to Treatment for Depression

PATIENT-RELATED FACTORS

- Under-recognition
- Underestimating the severity of illness
- Stigma of mental health disorder—reluctance to seek treatment
- Inability to seek treatment—lack of insurance
- Noncompliance to treatment

PROVIDER-RELATED FACTORS

- Under-recognition in primary care setting
- Lack of professional education or interpersonal skills
- Time constraints of practice
- Prescription of inadequate doses or duration of medications
- Underuse of other psychotherapeutic modalities

HEALTH CARE-RELATED FACTORS

- Lack of adequate insurance reimbursement
- Unavailability of psychotherapeutic practitioners
- Poor collaboration among interdisciplinary providers
- Poor continuity of care

TABLE 2

*The Diagnosis of Depression**

The diagnostic criteria for a major depressive episode include symptoms that persist for longer than two weeks and cause impairment in social and occupational functioning (a change from previous functioning).

- Depressed mood - feeling sad or blue**
- Anhedonia - loss of interest or pleasure in things previously enjoyed**
- Weight gain or loss - major changes in appetite
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Thoughts of death or suicide
- Feelings of worthlessness or guilt
- Reduced ability to concentrate, remember, think, or make decisions

*Diagnosis is based on the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Ed.) classification. Mood disorders, also called affective disorders, are comprised of two main groups: depressive disorders (depression alone) and bipolar disorders (depression and mania). Depression may also coexist with other psychiatric diagnoses.

** at least one of these first two symptoms must be present.

than placebos in European studies. Long-term studies and comparisons to existing antidepressants are lacking, as is a standardized preparation, but careful use by select patients could be supported, as side effects appear minor. St. John's wort should not be combined with prescription antidepressants without physician approval.

Antidepressants belonging to the serotonin specific reuptake inhibitors (SSRI) group are the most likely to cause sexual dysfunction in men and women (delayed orgasm or ejaculation, anorgasmia). The reported frequency of this bothersome side effect ranges from 9%-40%. The exact frequency is unknown, since women may be hesitant to discuss sexual problems, and diminished libido is also a symptom of depression. Decreasing the dose or taking a drug holiday—for example from Friday to Sunday—may help minimize sexual dysfunction, especially with paroxetine (Paxil™) or sertraline (Zoloft™), two SSRIs with shorter half lives. This treatment regimen is controversial and may result in withdrawal symptoms or noncompliance. Occasionally, yohimbine, buspirone (Buspar™), or amantadine is prescribed. Some clinicians advocate the use of ginkgo biloba, a Chinese botanical medicine, for sexual dysfunction induced by SSRIs. In some cases, a switch to an antidepressant in another drug class may be necessary.

Profile 3: Breast feeding allows transmission of many drugs to the infant, who has an immature metabolic system. Some clinicians advocate the use of sertraline if therapy with an SSRI is necessary, since little or no drug enters the breast milk, and there is no evidence of adverse effects on breast fed infants. Tricyclic antidepressants (TCAs) have a longer history of use in pregnancy and breast feeding. As with any medication used during pregnancy or breast feeding, benefits and risks must be individually assessed. (A recent study in the New England Journal of Medicine found TCAs and fluoxetine to have no effect on global IQ, language development, or behavioral problems in preschool children who had been exposed in utero.)

Each year, 30 percent of all new mothers, or more than 300,000 women, may show symptoms of post-partum depression, generally within four weeks of delivery. However, the occurrence of postpartum depression is probably underestimated.

Clinically diagnosable depression may occur at many different stages of women's lives, including prepartum, postpartum, after miscarriages, during infertility treatment, and at menopause. These are all times of changes in endocrine status. Mood changes and depressive symptoms are influenced by estrogen (and other hormonal) balance. The role of estrogen in women who present with signs and symptoms of depression during these times is not clearly understood and the subject of ongoing study.

Particularly during menopause, some women may be sensitive to low estrogen, or estrogen loss, and may find their mood more stable on estrogen replacement. Estrogen replacement is not an "antidepressant," and each woman must weigh her individual risks and benefits of estrogen replacement therapy with her physician. There is evidence for depressive symptoms, although not full depression, secondary to menopause.

Profile 4: Combining agents that act on the neurotransmitter serotonin and related receptors may cause serotonin syndrome, a drug-induced condition that can be life-threatening. Combining drugs that act on serotonin—such as diet pills, ergotamine, sumatriptan, meperidine, dextromethorphan, or l-tryptophan—with an SSRI can lead to this drug interaction. Signs and symptoms of serotonin syndrome include excitement, confusion, restlessness, agitation, fever, perspiration, motor weakness (ataxia), tremor, rapid heart rate, and hypertension. These can progress to loss of consciousness, requiring immediate medical assistance.

In recent years the amount of money spent on direct-to-consumer advertising of prescription drugs, including antidepressants, has increased dramatically. Whether this marketing strategy empowers or confuses consumers is debatable. This "pill for every ill" emphasis may mislead consumers into thinking a certain medicine is just what they need. Pharmacists are on the frontline here and have both the ability and responsibility to educate patients about their use of antidepressants and identify potential drug interactions, including those with over-the-counter agents.

Profile 5: Elderly people with depression generally have more physical symptoms and complaints (headache, chronic pain, constipation) than do younger individuals. Depression in the elderly may be harder to recognize and may accompany chronic diseases. Suicide rates are higher in the elderly. Cognitive symptoms may also be prominent—disorientation, memory loss, or distractibility.

Older people may have the "keep a stiff upper lip" attitude. It is not uncommon for families to consider depression a normal part of aging and its treatment unnecessary or futile. Pharmacists can help ensure that this misconception about depression is not perpetuated! A response to antidepressants in elderly patients may require 9-12 weeks of treatment at therapeutic doses. A patient or his or her family should avoid premature termination. Slower dosage titration may be necessary. However, not all geriatric patients need smaller doses as compared with younger individuals.

Gender and Depression

Women consume greater numbers of psychotropic medications than men, but drug development studies have historically relied on men (almost exclusively) as subjects. Even though the gap in medical research between men and women is starting to close, there is still not equality between the sexes in this area.

Both the National Institutes of Health and the Food and Drug Administration have established guidelines for clinical research to correct under-representation of women in medical and drug studies, but there are no gender-specific recommendations for the treatment of depression. One ongoing observational study, the Nurses Health Study, hopes to look at psychosocial factors such as mood changes, stress, anxiety, and social isolation that may influence women's health and longevity.

There is some general information available on the influence of gender on various pharmacokinetic parameters (see Table 5). Consideration of these factors when assessing the efficacy, toxicity, or dosing of antidepressant drugs in women may improve outcomes and minimize side effects.

TABLE 3

*Select Disease States and Drugs that May Contribute to Depression**

Medical Illnesses

Infections
- HIV/AIDS
- Pneumonia
- Neurosyphilis
- Mononucleosis
- Tuberculosis

Endocrine disorders
- Thyroid disorders
- Addison's/Cushing's disease
- Diabetes

Other
- Cardiovascular disease
- Malignancies
- Neurological disorders—Parkinson's, Huntington's, multiple sclerosis
- Alzheimer's disease
- Stroke
- Chronic pain syndrome
- Autoimmune disorders

Drugs
- Alcohol
- Antibiotics - sulfonamides
- Anticonvulsants - barbiturates, carbamazepin
- Analgesics - indomethacin , pentazocine
- Antihypertensives and cardiovascular agents - reserpine, clonidine, hydralazine, methyldopa, prazocin, beta-blockers, digoxin, procainamide
- Hormones - estrogen, glucocorticoids, progesterone
- Antituberculosis agents - ethambutol
- H2 Blockers
- Psychotropics - benzodiazepines, antiparkinsonians, chloral hydrate, phenothiazines
- Misc. - baclofen, levodopa, disulfiram

*Medical and psychiatric diagnoses coexist in many cases. It is important that medical and drug causes of depression are appropriately identified and treated or ruled out before antidepressant drug treatment begins.

TABLE 4*

Therapeutic Trial Timetable

Therapeutic Goal	**Timetable for response to medication** (relief from symptoms)
Sleep disturbance normalization, anxiety relief	1-2 weeks
Increased energy	2-3 weeks
Improvements in nervousness, somatic complaints, appetite disturbances	3 weeks
Mood elevation	4-6 weeks

* An adequate drug trial is 6 weeks at a therapeutic dose. Slow responders may take up to 10-12 weeks. Target symptoms should be assessed frequently—close friends or relatives may notice improvements first. Noncompliance is the primary reason for drug treatment failure. Patient education is a key to improving compliance. Careful attention to suicide risk is also important; however, women account for only 20% of completed suicides.

A Short Discussion of Antidepressant Drugs: A Heterogeneous Family

Effectiveness

All antidepressants are equally effective in relieving depression—a 60-80% response rate is generally reported. The search for an ideal antidepressant continues (see Table 6). With the introduction of newer drugs, progress has been made towards some ideal characteristics, but greater efficacy has not been achieved. Some antidepressants have utility in other related diseases (see Table 7).

Among the antidepressant drugs, there are tremendous differences in pharmacologic profiles, neurotransmitter effects, side effects, and cost.

Selection

Treatment should be individualized and based on the following patient and drug specific characteristics:

- family history of response (if any)
- prior patient response (if any)
- patient age and lifestyle considerations
- potential for side-effect tolerability
- potential for suicide—likelihood of overdose (see Table 8)
- convenience—once vs. multiple daily dosing
- medical and drug history—potential for drug interactions, disease state interactions
- desire for lab monitoring
- neurotransmitter effects
- cost

Generally, a single antidepressant is chosen, but occasionally, antidepressant combinations are utilized in refractory cases of depression. Combination antidepressant therapies, whether used to counter initial side effects on a short-term basis or as augmentation in long-term therapy, should be prescribed by one knowledgeable clinician.

Mechanism of Action

Antidepressant drugs interact in the brain with a number of neurotransmitters—specifically serotonin, norepinephrine, and dopamine. Our understanding of the mechanism of action of antidepressant drugs continues to evolve. We know that neurotransmitters, the receptors on individual cells or neurons, the enzymes that metabolize neurotransmitters, and even other substances such as peptides and hormones, all play interdependent modulatory roles in causing and alleviating depression. If a patient fails therapy with one antidepressant, it may be reasonable to choose another drug that has a primary action involving different neurotransmitters. The reader is referred to current literature for a thorough discussion of mechanisms of action.

TABLE 5

Gender Issues with Drug Use*

Factor**	Women Compared to Men	Effects
Gastric acid	less gastric acid secretion in women	unlikely to contribute to clinically significant differences in most drug absorption or bioavailability, but may accelerate absorption and increase bioavailability of TCAs, benzodiazepines, & antipsychotics
Gastric emptying	slower in women	slower absorption, delayed peak blood levels, lower peak blood levels of drugs are possible
Body mass	men weigh more, women have higher % body fat & less lean muscle mass	initial blood levels may be higher with drugs such as alcohol
Volume of distribution	may be increased in women	may lead to shorter duration of action and/or longer half-life with drugs such as benzodiazepines
Protein binding	slightly lower in women	unlikely to have clinically significant effects, except with warfarin
Metabolism	variable; liver and kidney function are important	estrogens & progestins inhibit liver enzyme activity; some CYP450 enzyme differences are important for cardiovascular drugs and benzodiazepines
Elimination	not well studied	gender differences in elimination are more likely due to differences in weight
Pregnancy		increase in clearance and rate of elimination of certain drugs, such as anticonvulsants and antibiotics and an increase in volume of distribution
Menopause		generally no clinically significant effects
Aging	generally less profound decline in age-related pharmacokinetic variables in women	liver enzyme activity and kidney function decline with age

*Exogenous hormones may exacerbate the gender-related pharmacokinetic differences. One-fourth of premenopausal and one-third of postmenopausal women take birth control pills or hormone replacement therapy.

** Phases of the menstrual cycle also affect these factors, but clinical significance is unknown. Steady-state plasma concentrations may fluctuate during the menstrual cycle and could possibly lead to decreased efficacy with some psychotropic drugs.

Costs

Drug cost differences (wholesale or acquisition costs) for months of treatment with different antidepressants can range from under twenty dollars to several hundred dollars. With the current emphasis on cost-containment, cost constraints may affect drug selection, whether patients belong to an HMO, have other traditional medical insurance, or have no medical insurance/drug coverage.

Drug selection should take into account more than the acquisition costs of medications. Pharmacoeconomic studies are examining benefits, costs, and outcomes of different treatment strategies. The total cost of care includes both direct (medicine, labs, MD visits) and indirect costs (lost productivity, family upheaval). Additionally, newer research is examining the short- and long-term benefits and quality of life measures. Identifying the most cost-effective therapy is the goal.

There is no general consensus as to the best antidepressant drug, and many agents claim first line status, but SSRIs are the most frequently prescribed antidepressant class of drugs.

Available Drugs

There is an impressive array of choices below for the pharmacological treatment of depression.

TCAs - tricyclic antidepressants

There are eight agents in the tricyclic class of antidepressants, an older, chemically-related group that has been extensively used and studied. The tertiary amines consist of amitriptyline (Elavil™), clomipramine (Anafranil™), doxepin (Sinequan™), imipramine (Tofranil™), and trimipramine (Surmontil™). The secondary amines are more popular and better tolerated due to their lower anticholinergic and orthostatic activity. (Anticholinergic side effects include constipation, blurry vision/dry eyes, urinary hesitancy, and dry mouth.) This group includes desipramine (Norpramin™)—the least anticholinergic TCA, nortriptyline (Pamelor™)—the least orthostatic TCA, and protriptyline (Vivactil™)—the least sedating TCA.

The ability to monitor therapeutic drug levels with most of the TCAs may be useful in assessing compliance, toxicity, and response. Since women may have higher serum levels than men, lower initial doses and conservative dosage increases should be the rule. TCAs can cause serious toxicity in an overdose: as little as two grams can be fatal. Cardiovascular effects, primarily conduction delay and arrhythmias, pose a risk in the elderly or individuals with heart block. The elderly may also be especially sensitive to anticholinergic side effects, including mental status changes and sedation (which is a contributor to falls/fractures).

Weight gain is common. Tolerance to sedation (which may be beneficial) and anticholinergic effects may occur with continued use. Additive sedative effects occur when a sedating antidepressant is given with another central nervous system (CNS) depressant. A once daily dose (at bedtime) is standard therapy, as is starting at low doses and using small increases to lessen side effects and to improve tolerability.

SSRIs—serotonin specific reuptake inhibitors

There are four agents in this class—fluoxetine (Prozac™), sertraline (Zoloft™), paroxetine (Paxil™), and fluvoxamine (Luvox™). All four drugs are associated with gastrointestinal (GI) complaints, although they are better tolerated than the TCAs. Headache, insomnia, and agitation can also occur. Paroxetine and fluvoxamine are slightly anticholinergic and slightly sedating. All of the SSRIs can cause sexual dysfunction. Weight gain is not usual with these agents (as compared to the TCAs, which frequently cause weight gain). Older patients may be especially sensitive to side effects such as diarrhea, anxiety, or loss of appetite.

The specificity with which these drugs work on the neurotransmitter serotonin (as compared to other classes of antidepressants with broader neurotransmitter effects) has revolutionized antidepressant drug treatment and helped clarify the modulator role serotonin plays in a number of conditions (e.g., sleep and eating disorders, autism, aggression, emesis, and migraines). It has also caused societal reflection and debate on whether, and to what extent, the human condition is biochemically determined.

All SSRIs have the potential to inhibit the liver enzymes responsible for the metabolism of many drugs (see Table 9). These interactions are the subject of ongoing study. There is no evidence that SSRI plasma levels correlate with the dose or the response to therapy.

The dosing of SSRIs is generally simpler than the gradual dose titrations that are used to reach a therapeutic dose with TCAs. Most SSRIs have a small dose range, if any, and therapy is typically initiated with a therapeutic dose in the great majority of patients.

MAOIs—monoamine oxidase inhibitors

There are two agents in this class—phenelzine (Nardil™) and tranylcypromine (Parnate™). These drugs are rarely the first choice for the treatment of depression. They are primarily reserved for refractory or atypical cases of depression, where such symptoms as increased sleep and appetite, tension, phobias, or increased depression in the evening are present.

Careful selection of patients and good compliance with MAOI regimens are important in order to minimize toxicity with these agents. Tyramine dietary restrictions are particularly important to avoid a potentially fatal interaction with MAOIs. Daily divided doses are usually necessary, rather than a single daily dose as is used with TCAs and SSRIs. Drug interactions with meperidine, sympathomimetics, or serotonergic agents can lead to serious toxicity.

TABLE 6

Characteristics of an Ideal Antidepressant

- rapid onset of action
- convenient daily dosing
- minimal/no side effects
- no drug interactions
- safety in overdose
- patient response correlates with blood level
- activity in a range of depressive disorders
- low cost

TABLE 7

Drug Treatment for Depression

Selected antidepressants and FDA indications

Name	Depression	OCD*	Other
Clomipramine		+only	
Fluoxetine	+	+	bulimia
Sertraline	+	+	
Paroxetine	+	+	panic disorder
Fluvoxamine		+only	
Bupropion	+		smoking cessation

*OCD = obsessive compulsive disorder

TABLE 8

Factors for High Suicide Risk

- advancing age
- unemployment
- recent loss
- coexisting substance or alcohol abuse
- family history of suicide
- living alone
- lack of social support

TABLE 9

Drug Interactions of Newer Antidepressants with Liver Enzyme Systems

Enzyme@	Inhibitor Drug#	Common Substrate Drugs*
1A2	Fluvoxamine	Imipramine, Theophylline, Caffeine, Clozapine, Acetaminophen, Warfarin
2C9	Sertraline, Fluoxetine	Warfarin, Phenytoin, NSAIDs
2C19	Fluvoxamine	Imipramine, Propranolol, Diazepam
2D6	Fluoxetine, Paroxetine, Sertraline	Desipramine, Nortriptyline, Clozapine, Haloperidol, Thoiridazine, Beta-blockers, Risperidone, Codeine, Hydrocodone
3A4	Fluvoxamine, Fluoxetine, Sertraline, Nefazodone	Imipramine, Alprazolam, Midazolam, Triazolam, Clozapine, Terfenadine, Astemizole, Cisapride, Carbamazepine, Calcium Channel Blockers, Fluconazole, Ketoconazole

@ family, subfamily, and gene designations

#with moderate to high inhibitory potential

* Blood levels or effects of these drugs can be enhanced with concurrent administration of inhibitor drugs; greatest potential for toxicity occurs when therapy is started (first week), stopped, or dosage is changed. Patients at greatest risk are the elderly and those with hepatic dysfunction or genetic predisposition. It appears that not everyone shares the same types and concentrations of the approximately 30 closely related enzyme systems. For example, up to 25% of Asians may lack some enzyme function in the 2C class. Caucasians are four times more likely to be poor metabolizers in the 2D6 system than Blacks or Asians.

TABLE 10

Risk Factors for Depression Recurrence

- family history of recurrent major depression or bipolar illness
- two or more episodes of depression
- early onset (before age 20) or older age of onset (age 50-60)
- significant anxiety
- inadequate social support
- recent, current, or anticipated stressors
- substance abuse
- seasonal pattern

Miscellaneous older (second generation) agents

This group of antidepressants includes amoxepine (Ascendin™), maprotiline (Ludiomil™), trazodone (Desyrel™), and bupropion (Wellbutrin™). Amoxepine and maprotiline have very limited usefulness due to renal and neurologic toxicity (amoxepine), the potential for overdose toxicity (maprotiline), and the potential for seizures (maprotiline and amoxepine).

Trazodone is less likely than the TCA group of drugs to impair cardiac conduction and does not have anticholinergic side effects. The sedative effect of trazodone is sometimes used during initial SSRI treatment if insomnia is a problem. A rare side effect of trazodone is priapism. Trazodone usually requires multiple daily dosing.

Bupropion has low cardiovascular, anticholinergic, and sedative effects. It may have stimulant effects. There is little or no evidence for drug interactions with bupropion, and it causes little sexual dysfunction. Bupropion is associated with an increased risk of seizures, particularly with higher doses. It has recently been given FDA approval (under the brand name Zyban™) as a smoking cessation aid.

Miscellaneous newer agents

Nefazodone (Serzone™), venlafaxine (Effexor™), and mirtazapine (Remeron™) are newer antidepressants that do not fit into the antidepressant classes discussed above. Nefazodone is structurally related to trazodone, requires twice daily dosing, and may cause dizziness, nausea, and hypotension. Its sedative quality may be an advantage for patients with anxiety or insomnia. Nefazodone causes little or no sexual dysfunction.

Venlafaxine has little cardiovascular toxicity, low toxicity following an overdose, and may be beneficial in resistant cases of depression. Multiple daily dosing is required. The major side effects of venlafaxine include GI complaints, dizziness, sedation, sweating, tremor, hypertension, and sexual dysfunction. It does not appear to cause weight gain.

Mirtazapine is the newest agent available and may have antianxiety as well as antidepressant activity. This agent causes sedation, tremor, weight gain, and increased liver enzyme and lipid levels.

Length of Drug Treatment

Drug treatment generally continues for 6-9 months after a positive response has occurred. The dose that achieved remission is usually considered the maintenance dose, although lower doses have been used. About 50% of patients with depression have a recurrence sometime during their life. Therefore, some individuals may need ongoing maintenance treatment, especially those with risk factors for recurrence (see Table 10).

When drug therapy is discontinued, a slow dose taper should be utilized to minimize the risk of recurrence and withdrawal effects. TCAs should be tapered over 3-4 weeks (at the very minimum), and SSRIs should be tapered over 1-2 weeks. A withdrawal syndrome, which may last a week or more, occurs in a number of patients when TCAs, MAOIs, or SSRIs are discontinued. The reported incidence of withdrawal syndrome varies from 20% to more than 80% and depends, to

continued on page 44

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Learning Objectives: After reading this article, participants should be able to:

FOR OSTEOPOROSIS:
- Describe the socioeconomic impact of fractures related to osteoporosis.
- Compare and contrast the various drug therapies currently used for the treatment of osteoporosis.

Update on Osteoporosis

Jane Takagi, Pharm.D.
University of Southern California/Kenneth Norris, Jr., Cancer Hospital and Research Institute
Assistant Professor of Clinical Pharmacy, University of Southern California School of Pharmacy

— Practice Pearls —

- Ensure adequate daily intake of calcium (1000 mg-1500 mg) and vitamin D (400 IU-800 IU)
- Exercise
- Long-term use (more than 10 years to life-long) of hormone replacement therapy is necessary for maximum bone benefit.
- The recommended dose of alendronate for the treatment of osteoporosis is 10 mg per day. Take alendronate on an empty stomach with a full glass of plain water. Remain upright for at least 30 minutes to minimize esophageal irritation.
- The recommended dose of nasal calcitonin for the treatment of osteoporosis is 200 IU per day, alternating nostrils to minimize nasal irritation.
- No matter what pharmacologic intervention is used (HRT, biphosphonates, calcitonin, or fluoride), ensure adequate calcium and vitamin D intake or supplementation.

Introduction

Osteoporosis is the most common metabolic bone disease and affects 25 million Americans, of which 80% are women. Postmenopausal women are identified as the group most at risk for osteoporosis; however, it can occur in both men and women with advancing age, or it may be drug-induced. This article will briefly review osteoporosis and comment on the newer drugs available for prevention and treatment.

Nature of Osteoporosis

Bone affected by osteoporosis is described as "porous" and is characterized by low mass and structural deterioration. This leads to bone fragility and an increased susceptibility to fractures.[1] Until a fracture occurs, bone loss typically proceeds without symptoms. Fractures may occur at any skeletal site, but are most common at the spine, hip, and wrist. Vertebral (spinal) fractures may cause back pain, loss of height, or deformities such as "dowager's hump." Painful and debilitating hip fractures cause most of the disability and death associated with osteoporosis.

Impact of Osteoporosis

The socioeconomic impact of fractures related to osteoporosis includes physical disability, loss of independence, and a tremendous economic cost. Of individuals who experience a hip fracture, 50% will require assistance after leaving the hospital, and 25% will require care in a nursing home. Individuals suffering hip fractures have a 5-20% greater risk of dying within the first year following that injury than others in their age group.[2] Estimated national direct expenditures for osteoporosis and related fractures, including the cost of hospitalization, surgery, and nursing home care, are at least $10 billion annually, and the cost continues to rise.[2]

Diagnosis

Diagnosis of osteoporosis often occurs after a fracture. Screening may identify individuals at risk, but at this time screening is not widely available and is not considered cost-effective. Bone mineral density (BMD) is an indirect measure of bone strength and is associated with the likelihood of fracture. BMD can be measured noninvasively by using dual energy X-ray absorptiometry (DEXA). DEXA can measure bone mass at any site in the skeleton with a precision that is within 1-2% of actual bone mass.[2] The World Health Organization (WHO) Classification provides a practical definition for osteoporosis based on BMD. Normal BMD is defined as a value within 1 standard deviation (SD) of the average BMD for young normal adults. Low BMD or osteopenia is defined as a value between 1 and 2.5 SD below the young normal average. Osteoporosis is defined as a BMD value 2.5 SD below the young normal average. Severe osteoporosis is a bone density

more than 2.5 SD below the average and a history of nonviolent bone fracture.[1,2] Based on this classification, one of nine postmenopausal women (age 60-70) have normal BMD, approximately 30-50% have osteoporosis, and women in the remaining group have osteopenia.[1]

Clinical Consequences

The clinical consequence of osteoporosis is bone fracture. Osteoporosis is responsible for more than 1.5 million bone fractures annually that are nonviolent in nature.[1,2] The lifetime risk of a clinically evident spine, hip, or wrist fracture is approximately 40%.[1] The incidence of bone fracture is low until age 50 and then rises exponentially with advancing age.[1] Risk factors for osteoporosis are listed in Table 1. Without a baseline BMD measurement, it is difficult to predict which individuals are at highest risk for osteoporotic fractures.

Factors in Bone Mass

The maintenance of bone mass is a dynamic process of growth, balance, and gradual decline. With age, bone formation (mediated by bone building cells called osteoblasts) occurs more slowly than bone resorption (mediated by bone removing cells called osteoclasts), resulting in a net loss of bone mass with each cycle.[3] The risk of osteoporosis is influenced by peak bone mass, rate of bone loss, and microarchitectural deterioration. An individual's peak bone mass is achieved by age 35 and is influenced by genetics, diet, and exercise. Weight-bearing exercise and adequate dietary intake of calcium and vitamin D during the ages ranging from adolescence to 35 years are important for achieving maximal peak bone mass. Bone mass decreases more rapidly in women than men because they have less bone to begin with; at menopause, loss of estrogen also enhances bone loss. Bone loss related to aging (in both men and women) results from decreased bone formation.[3] Microarchitectural deterioration of bone leads to decreased bone density and decreased bone strength.

Management of Osteoporosis:

1. **Goal** The goal of managing osteoporosis is fracture prevention; there is no cure. Given that osteoporosis is a disease that becomes more prevalent with age, it is reasonable to take steps to prevent or minimize bone loss throughout adulthood.
2. **Available Drug Therapy** Currently, drugs for the treatment of osteoporosis primarily produce antiresorptive activity. Thus, treatment prevents further bone loss, but does not substantially increase BMD (increases are in the range of 2-7%).[4] All pharmacologic interventions should include adequate dietary or supplemental calcium intake (1000 mg-1500 mg per day) and vitamin D (400 IU-800 IU per day). Weight-bearing exercise (walking, running, aerobic activity) provides additional bone strengthening and improves balance, which may reduce the risk of a fall.

Hormone Replacement Therapy (HRT)

HRT is the current standard and most cost-effective pharmacotherapy for preventing and treating osteoporosis in postmenopausal women. Rapid bone loss of 2-4% per year occurs with menopause due to the reduction in estrogen levels. Although this rapid bone loss levels off after five to ten years, age-related bone loss persists. HRT reduces bone resorption. The exact mechanism is unclear, but the binding of estrogen to receptors on bone appears to reduce both bone turnover and bone loss. This antiresorptive activity is mediated by osteoclasts and may also be influenced by cytokine activity and parathyroid hormone.

HRT typically consists of oral conjugated estrogens 0.625 mg daily or transdermal estradiol 0.05 mg patches applied twice weekly for 25 days, with a progestin for 10-13 days each month at the end of the cycle.[5] A higher dose of estrogen than that required to control menopausal symptoms may be necessary for bone protective effects.

By decreasing the rate of bone loss, estrogen maintains or slightly increases BMD. The magnitude of effect is 1-3% each year in the initial years of therapy after menopause.[5] This averages to an overall increase in BMD of 5-10%. HRT reduces the vertebral fracture risk by approximately 40-50%, and the nonvertebral fracture risk by approximately 25%.[5] The bone protective effect is maintained only during the time period that HRT is taken, and bone loss resumes once therapy is discontinued.

Arguments can be made for either initiating therapy at menopause or delaying HRT until age 60.[4] Beginning HRT (or unopposed estrogen if the individual has had a hysterectomy) just after menopause and up to five years later is convenient and effective in reducing the rapid bone loss related to menopause. Women who are at increased risk for osteoporosis (see Table I) should consider beginning HRT when menopause occurs. To achieve the maximal bone benefit and reduction of fracture risk, HRT must be taken for at least 7-10 years, and perhaps indefinitely.[5] However, the symptoms of menopause (e.g., hot flashes) generally resolve within a few years, and after this point, compliance with HRT is usually poor.

The greatest risk for bone fracture is advancing age (75-80 years). One in six women will suffer a hip fracture in her lifetime.[4] Fortunately, even if a woman delays HRT until age 65-70, it is still beneficial for reducing the risk of hip fracture. HRT still has a positive effect, but it is not as significant (in terms of increased BMD) as when therapy is started earlier in the postmenopausal period.

The controversy surrounding acceptance of HRT is related to cancer risk. The risk of endometrial cancer is increased in women with an intact uterus who take unopposed estrogen. The increased risk of endometrial cancer can be prevented with concomitant use of progestins for 10-13 days a month.[5] The effect of HRT on breast cancer risk is controversial and unclear. There is a slightly increased risk for developing breast cancer among individuals who have received HRT compared to individuals who have never taken estrogens.

If a woman is undecided or reluctant to begin HRT, she should consider her menopausal symptoms, coronary heart disease risk, and history of, or risk of, breast cancer. In general, the risk of hip fracture is equal to the combined risk of developing breast, uterine, and ovarian cancer. In an individual who is intolerant of HRT, consider her age (>50-60 years), number of risk factors for osteoporosis and BMD (hip). If the individual has a low BMD and risk factors for osteoporosis, an alternative therapy (discussed below) may be offered.

Future directions

Raloxifene has just been FDA-approved for prevention of osteoporosis in postmenopausal women. Raloxifene is a selective estrogen receptor modulator (SERM). SERMs selectively stimulate bone and cardiovascular tissue but not breast and uterine tissue. Thus, one benefits from the positive estrogen effects on bone (inhibit bone resorption) and cardiovascular (lipid profile) system without the serious estrogen-related adverse effects (cancer risk) and eliminates the need for concomitant progestins use in women with a uterus. The recommended dose of raloxifene is 60 mg daily.

Bisphosphonates

Alendronate

Alendronate is a new, potent bisphosphonate which inhibits osteoclast-mediated bone resorption by binding to bone.[6,7] Alendronate was FDA-approved in October 1995 for the treatment of osteoporosis in postmenopausal women and has been marketed as the first nonhormonal therapy for osteoporosis. It serves as an alternative for individuals who cannot tolerate estrogens.

Bisphosphonates can inhibit both bone resorption and bone mineralization. Etidronate is a nonselective, less potent bisphosphonate that must be administered cyclically to avoid mineralization defects and osteomalacia.[6] The effects of etidronate on bone mass are most pronounced in the first 6-12 months of therapy, then are progressively less evident in the second and third years of use. Alendronate decreases bone loss by selectively increasing BMD in a dose-dependent manner. Unlike etidronate, the doses of alendronate used to increase BMD do not impair bone mineralization.

The recommended dose of alendronate for the treatment of osteoporosis is 10 mg daily. The patient should take it on an empty stomach with a full glass of plain water (avoiding coffee, juices, carbonated drinks) in the morning to maximize absorption. Due to its potential for causing esophageal irritation, the patient must stay upright (not lie down) for at least 30 minutes after taking a dose. Calcium supplements, antacids, and food can decrease alendronate absorption. The administration of alendronate should be separated from that of other medications and food by at least 60 minutes.

Alendronate is well tolerated. The most frequently reported adverse effects are gastrointestinal in nature and include abdominal pain, nausea, upset stomach, constipation, diarrhea, and flatulence. Infrequently, musculoskeletal pain and headache have been reported.

Several randomized, double-blinded, placebo-controlled trials have evaluated the safety and efficacy of alendronate in postmenopausal osteoporotic women.[7-10] Alendronate prevents bone loss and increases BMD in a magnitude similar to that reported with HRT (5-10%) and restores bone turnover to rates similar to those in normal premenopausal women.[7-10] Alendronate reduces the risk of vertebral fractures by approximately 40-50% and that of nonvertebral fractures by 20-30%.[7-9]

BMD changes appear more closely related to the daily dose than to the cumulative dose, as seen when individuals given 10 mg daily for the treatment period are compared to individuals given high dose alendronate (20 mg-40 mg) for three months followed by low dose alendronate (5 mg).[7] In one trial, the increase in BMD during the first year of treatment persisted during the subsequent year, suggesting that the effects of alendronate are sustained following discontinuation. This is in contrast to the prompt decreases in BMD that are seen with the discontinuation of estrogen and calcitonin therapy.[7] The cumulative long-term effects of alendronate are unknown and are currently being evaluated.

The Fracture Intervention Trial

This large, randomized and controlled trial, was designed to evaluate the effect of alendronate on the frequencies of vertebral and nonvertebral fractures in postmenopausal women with low bone mass.[10] Women were divided into two groups based on presence or absence of an existing vertebral fracture at time of recruitment. Black et al. have reported early findings from the group of women with an existing vertebral fracture at the time of recruitment. This group represented those at highest risk for subsequent fractures and was divided into a treatment (alendronate) and placebo group. The women in the treated group received alendronate 5 mg daily for 24 months and 10 mg daily thereafter. Preliminary findings showed such significant reduction in fracture risk that the investigators closed this arm of the trial so that women in the placebo group may benefit from alendronate as well. As with other alendronate studies, BMD measurements increased at the spine, hip, and other skeletal sites. Follow-up radiographs showed that the risks of new vertebral, hip, and wrist fractures were reduced by 47%, 51%, and 41%, respectively.

Clearly, alendronate is a promising antiresorptive agent that is indicated for treatment and prevention of osteoporosis.

Calcitonin

Calcitonin is a hormone secreted from the parafollicular cells of the thyroid gland. It plays a regulatory role in calcium and phosphorus homeostasis and

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TABLE 1

Risk Factors for Osteoporosis

- Estrogen deficiency
- History of fracture after age 50
- Advancing age
- Diet low in calcium, vitamin D
- Physical inactivity, bedridden
- Thin and or small frame
- Family history
- Smoking history
- Corticosteroid use

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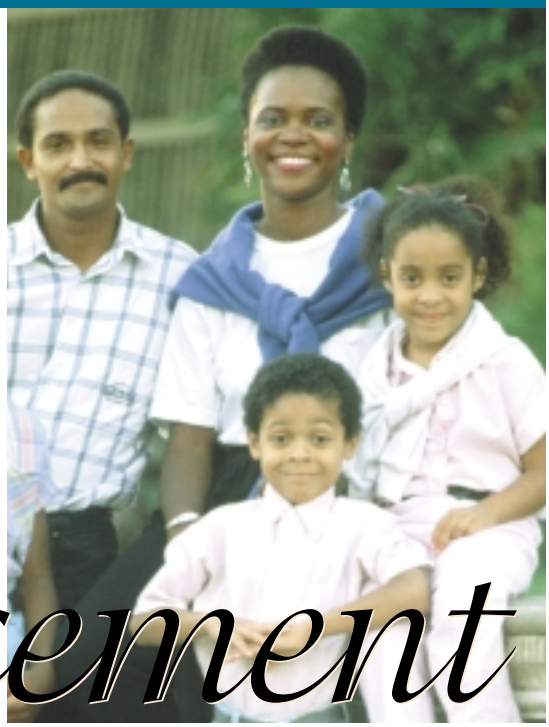

Hormone Replacement Therapy

By Leslie Shimp, Pharm.D., M.S.
Associate Professor of Pharmacy, College of Pharmacy, University of Michigan
Consultant pharmacist, Department of Family Practice, Medical School, University of Michigan

Weighing the Benefits and Risks

This article is excerpted from two articles originally published in The Rx Consultant, Vol. VI, No. 9 and Vol. VI, No. 11 (Copyright 1997, Continuing Education Network, Inc.) and is reprinted with permission. ***To receive a complimentary, full text copy of Vol. VI, No. 9, "Menopause and Hormone Replacement Therapy," call 1-800-798-3353.***

Overview

In the United States today there are about 40 million women who are postmenopausal; every year another 3.5 million women reach the age of menopause. With an average life span of 81 years, women live about one-third of their lives after menopause occurs. The estrogen deficiency of menopause causes early symptoms such as hot flashes, irregular menstrual cycles, sleep disturbances, vaginal dryness and urinary incontinence. Long-term consequences of estrogen deficiency include an increased risk for heart disease and osteoporosis.

"Should I take estrogen at menopause?"

Every year millions of women ask this question, only to learn there is no simple yes or no answer. Hormone replacement therapy (HRT), which is a combination of estrogen and progestin therapy, can have both positive and negative consequences, and many women are confused about the potential benefits and risks.

One reason for this confusion is the lack of accurate information about HRT. A study of female college graduates found that most did know HRT could reduce the risk of heart disease and osteoporosis, and increase the risk of breast cancer. However, twice as many women were worried about breast cancer as were worried about heart disease. For most of these women, the relative lack of concern about heart disease is in sharp contrast to the facts. Only 1% of the women described themselves as being at risk for heart disease, when in reality 20% develop it by the age of 70.[1] The result of confusion about the benefits and risks of estrogen replacement is that few women opt to use it. Even though the benefits are widely publicized, only 15-25% of American women start HRT, and even fewer continue it long-term.[2]

The decision to use HRT is a personal one, in which each woman must weigh her potential benefits against the possible risks. An abundance of ongoing research in this area further complicates the decision for many women.

This article discusses what is currently known about the benefits of HRT for early menopausal symptoms, heart disease and osteoporosis. Intriguing preliminary data about the role of estrogen in Alzheimer's disease is included. We then present up-to-date information on the major risks of HRT: breast cancer and endometrial cancer.

What do we know about the positive long-term effects of HRT?

Current information suggests that many postmenopausal women benefit from therapy. One study has shown a 40% reduction in death from all causes among women who had taken estrogen for 15 or more years.[4] However, data from population studies cannot be directly applied to the individual.

What should a woman consider when deciding for or against HRT?

In deciding about hormone use, each woman should consider her own risk for heart disease, osteoporosis and breast cancer. Clarifying the goal(s) of therapy also helps. For example, if the goal is to relieve menopausal symptoms

like hot flashes, HRT will be short-term, and breast cancer can be largely disregarded as a concern. However, if hormone replacement is being considered for prevention of heart disease or bone fractures, therapy must be long-term, and the risk of breast cancer is greater.

Can HRT prolong life?

In general, current evidence suggests that most women will live longer with HRT. It has been estimated that less than 1% of healthy perimenopausal women would not benefit from HRT.[3]

Do some women have more to gain from HRT than others?

Women who have had a hysterectomy and those who are at risk for heart disease are most likely to benefit from HRT. Women who are at low risk for heart disease but have an increased risk for breast cancer are poor candidates for HRT. However, most women do not fit into these categories, and the benefits/risks are less clear.

How can a woman get additional information about HRT?

Reliable information can be obtained from several books and a variety of organizations. Telephone numbers and internet addresses of organizations that provide useful information are listed in the inset on page 37. Additionally, two texts that may be useful for pharmacists, as well as for individuals, are:

- *Dr. Susan Love's Hormone Book* (Susan Love, M.D., Random House, New York, 1997)
- *A Woman Doctor's Guide to Hormone Therapy: How to Choose What is Right for You* (Nananda Col, M.D., Tatnuck Booksellers Press, 1997)

Symptoms and Consequences of Menopause

A decline in circulating levels of estrogen is associated with the classic symptoms of menopause: disturbances of menstrual pattern, hot flashes/hot flushes, sleep disturbances, psychological symptoms and atrophy of the urinary and genital tracts. Hot flashes occur in up to 75-85% of U.S. women and commonly persist for 2-5 years.[5,6] Urogenital atrophy is a common result of estrogen deficiency which eventually affects most women. Symptoms of vaginal atrophy include vaginal dryness, itching and burning, and discomfort with sexual intercourse. Atrophy of the urinary tract may lead to urinary urgency and stress incontinence. The two conditions associated with a decline in circulating estrogen which have the greatest impact on women's health are osteoporosis and coronary heart disease. Over 90% of people with osteoporosis are postmenopausal women. It is estimated that 25-44% of women experience osteoporotic bone fractures after menopause. Cardiovascular disease is the leading cause of death for women in the United States, and the incidence of cardiovascular disease increases markedly after menopause. Over 53% of postmenopausal women will die of cardiovascular disease.[7]

Hormone Replacement Therapy

The primary benefits of postmenopausal hormone therapy are derived from estrogen (estrogen replacement therapy, or ERT). Estrogen is the hormone associated with the relief of menopausal symptoms, increased bone density, and reduction in the risk for heart disease. A progestin is added to protect against the increased risk of endometrial cancer caused by the use of estrogen alone in women with a uterus. The combination of estrogen and progestin is what is referred to as HRT. Progestin therapy is not necessary if a woman has had a hysterectomy.

Therapeutic Uses

Disturbances in Menstrual Patterns

Perimenopausal irregularities in menses may sometimes be managed with oral contraceptives[8,9] or intermittent regimens of a progestin (e.g., medroxyprogesterone acetate).

TABLE 1

Management of Common Adverse Effects of Postmenopausal HRT

Adverse Effect	Management
nausea	• take medication with food or at bedtime • gradually increase estrogen to a maintenance dose • switch to a different estrogen or different route of estrogen administration (e.g., transdermal)
breast tenderness	• reduce the estrogen dose • switch to transdermal estrogen • switch to a different progestin • use a C-21 progestin (MPA) • limit caffeine intake • add a diuretic, evening primrose oil, or vitamin E
vasomotor symptoms	• increase the estrogen dose • switch to transdermal estrogen
heavy withdrawal	• decrease the estrogen dose • switch to a continuous progestin dosing regimen
bleeding	• use a 19-nortestosterone progestin (norethindrone or norethindrone acetate)
headaches	• if migraine-like, consider discontinuing therapy • switch to continuous estrogen therapy • switch to transdermal estrogen
bloating	• switch to a different progestin • lower the progestin dose • add a diuretic on days of progestin, or for 7-10 days prior to menses
mood alterations	• switch to a different progestin • decrease the progestin dose • switch to continuous progestin dosing • add a diuretic
decreased libido	• add androgen to the regimen

Hot Flashes/Hot Flushes

Estrogen is effective for the treatment of hot flashes, with a 95% success rate after 3-4 weeks of therapy.[5] If hot flushes during the night and sleep disturbances occur, estrogen therapy will decrease night sweats and increase REM sleep. Usually, a daily dose of 0.625 mg of conjugated equine estrogen (CEE) will alleviate hot flashes; occasionally a higher dose may be required.[10,11] If estrogen is contraindicated, progestin therapy may be used. Both oral (10-20 mg/day) and depo (50-150 mg/month) medroxyprogesterone acetate (MPA) and oral megestrol acetate (40 mg/day) have been effective.

Clonidine has been used as a nonhormonal therapy for hot flashes. Both oral and transdermal dosage forms have been used, usually in doses of 0.1-0.2 mg/day. Some information suggests that doses above 0.1 mg/day are necessary.[12] The effectiveness of clonidine is controversial, and, at best, a modest improvement in the frequency or severity of hot flashes. Clonidine is less effective than either estrogen or a progestin. Transdermal therapy is likely to be better tolerated than oral therapy.[13] There is little evidence to support the use of Bellergal™ (phenobarbital, ergotamine and belladonna alkaloids), an agent with many potential adverse effects.[12]

Recently, plant estrogen sources (phytoestrogens or isoflavones) have become popular as a way of managing hot flashes. Many plants, such as citrus fruits, grapes, and red clover sprouts contain phytoestrogens but in unknown and generally small quantities. The two food products most advocated as dietary sources of estrogen are soy products (tofu, soy flour, soy milk, soy beans) and flaxseed; a recipe book utilizing these products is available.[14] Although these plants may be useful for managing hot flashes, it is unclear if any of estrogen's other benefits will be gained by ingesting phytoestrogens. Additionally, while phytoestrogens might stimulate the endometrium, increasing a woman's risk for endometrial cancer, it has been suggested that soy products offer some protection against breast cancer.[14]

Cognitive Symptoms and Dementia

Evidence is accumulating that changes in estrogen levels with menopause may affect cognitive function. Estrogen has been found to promote the growth and survival of cholinergic neurons,[15,16] promote regeneration or repair of damaged neurons,[15,17] increase cerebral glucose utilization,[18] prevent amyloid deposition,[16] increase cerebral blood flow,[17,18] and increase cholinergic function.[19] The cholinergic system, including the neurotransmitter acetylcholine, is the most important system for memory and cognitive functions. Studies comparing the performance of postmenopausal women using estrogen to nonusers found that users performed better on some tests, such as those of verbal memory, conceptualization, and the capacity for learning new information.[20-22] Other mental functions (e.g., visual memory) were not affected by estrogen use.[21] The effects of estrogen were modest, and there is no evidence that women who do not take estrogen are "impaired" to the extent that daily functioning is affected.[15]

Women make up the majority of persons with Alzheimer's disease.[18,23] It is hypothesized that the decrease in estrogen with menopause may increase a woman's risk for dementia.[17,18,24] Several effects of estrogen within the brain may prevent or delay the onset of dementia.[16-18] Aside from familial Alzheimer's disease, dementia is uncommon in the first two decades after menopause, but by the third decade up to half of women have some clinical signs of dementia.[15] Two studies suggest that the risk of Alzheimer's disease is lower (by 30% in one study and 60% in the other) among estrogen users than nonusers.[16,24] In addition, several small studies of patients with Alzheimer's disease have shown that estrogen therapy improves cognitive test scores and cognitive function in some patients.[25,26] While the information accumulated to date is intriguing, it is also limited. Further study is necessary to determine whether estrogen protects against dementia or is useful for persons with dementia.

Urogenital Atrophy

In general, the vaginal and urinary symptoms of menopause are very responsive to estrogen therapy, improving 50-70%.[5] The dosage of estrogen required to treat these symptoms is usually less than that required for the management of hot flashes. Therapy can be either oral (0.3-0.625 mg CEE) or vaginal (cream or vaginal ring). Topical therapy with a vaginal cream is initiated with daily application for 4 to 8 weeks, then tapered to several times per week or just several times per month. In many cases, women can stop therapy after six months. A progestin is generally not prescribed with intermittent use of estrogen cream. If use is more frequent or continued long term, a progestin should be added for endometrial protection.[27] Estring™, a new vaginal delivery system, is inserted into the upper third of the vagina where it remains for 90 days. Minimal systemic absorption occurs with Estring™, and progestin therapy is not required. During the perimenopausal period, when pregnancy protection may still be needed, low dose oral contraceptives may relieve symptoms.[9]

Non-hormonal therapy for urogenital symptoms also exists. Vaginal lubricants (e.g., Gyne-Moistrin™, Replens™) can be used to manage dryness and/or discomfort with sexual intercourse. The initial dosage of lubricant is two tablespoonsful inserted vaginally, then the application frequency and quantity can be adjusted according to patient needs. Pelvic floor exercises may be useful for the management of urinary incontinence.[28]

Osteoporosis

Estrogen therapy reduces the risk of osteoporosis and related fractures. The risk for spinal fractures is reduced 50%, and the risk for fractures of the hip and forearm is reduced 25%.[7] Estrogen prevents bone loss, primarily by suppressing bone resorption. In women with osteoporosis, this allows bone building cells to "catch up" with bone resorbing cells, and bone mineral density increases by 5-10%.

Bone loss occurs as a result of aging, and there is also an accelerated phase of bone loss at the time of menopause. Estrogen is the only agent which has been documented to protect against the accelerated phase of bone loss.[29,30] The effect of estrogen on bone resorption is lost if therapy is stopped. Women who stop taking estrogen within several years of menopause may revert to a hip fracture risk similar to that of

— Facts for Patients —

- A decision on the use of HRT should be individualized. Information from the literature helps to provide a sense of the potential benefits and risks, but this must be combined with personal health information, as well as health beliefs and concerns, to form the basis for a decision. Evaluation of existing risk factors for osteoporosis and heart disease also provides useful information for the woman considering HRT.
- The goal of postmenopausal hormone replacement therapy is to replace estrogen. Progestin therapy is added to estrogen therapy in women who have a uterus (i.e., have not had a hysterectomy). The progestin therapy protects them from an increased risk of endometrial cancer, which can be caused by the use of estrogen alone.
- HRT has two major health benefits:

  Prevention of heart disease: Heart disease is the leading cause of death for women, and estrogen therapy reduces the likelihood of a woman developing heart disease by about 35-50%.

  Prevention of osteoporosis: Estrogen use reduces the likelihood that a woman will develop osteoporosis; bone fractures of the spine are 50% less likely and hip fractures are 25% less likely in women taking hormone therapy.
- The greatest concern with postmenopausal hormone therapy is the development of breast cancer:
  - Little increase in breast cancer risk occurs for women who take hormones short term (5 years or less) for the treatment of menopausal symptoms.
  - The risk increases by 30-50% for women who use hormones long term (10 or more years) to prevent osteoporosis and heart disease. Nonetheless, the risk for breast cancer remains lower than the risk for heart disease for most women.
- Side effects are not uncommon with HRT, but they can usually be minimized or avoided by changes in therapy. Menstrual-like bleeding can be eliminated by some HRT regimens. Changing the hormone doses can decrease common side effects such as heavy bleeding, bloating and breast tenderness.

women who never took postmenopausal estrogen.[7] The majority of bone fractures occur in women over the age of 80, and most hip fractures occur very late in life. In order to sustain a bone protective effect into late life, at least 7 years of postmenopausal estrogen therapy is required.[31] Optimal protection of bone occurs when estrogen is started at the time of menopause and continued long-term.

However, even if estrogen therapy is started 15 years after menopause, the protection against osteoporosis-related fractures may be very close to that seen for women who began therapy at menopause and continued it into old age.[32,33] Bone loss and the beneficial effect of estrogen on bone continue into late life.[30,32] Estrogen therapy can be initiated to prevent or treat osteoporosis many years after menopause. In fact, recent data suggest that older women may show a greater response to estrogen in terms of increased bone density than do perimenopausal women.

Any estrogen therapy which achieves adequate circulating levels of estrogen (a serum estradiol level of about 40-60 pg/ml)[5] will protect against osteoporosis and bone fractures. This requires a daily dose of 0.625 mg CEE or the equivalent. A dose of 0.3 mg partially inhibits bone loss, and a dose of 1.25 mg offers no additional protection. Transdermal therapy (50-100 mcg estradiol) also has protective effects.[34] The combination of estrogen and progestin has a similar effect on bone to estrogen taken alone.[7] While estrogen replacement is considered the mainstay for osteoporosis prevention and treatment, nonhormonal measures also reduce the risk of this disease. These include adequate calcium and vitamin D intake, weight bearing exercise, and avoiding cigarette smoking and excessive alcohol intake. Recently, the FDA approved alendronate (Fosamax™), which inhibits bone resorption, for use as a preventive agent. The dose of alendronate for preventive use is 5 mg per day.

Coronary Heart Disease

Many observational studies have reported a cardio-protective effect from estrogen. It is estimated that estrogen therapy reduces the risk of heart disease 40-50% in postmenopausal women. The greatest benefit appears to be for current users, although some risk reduction persists for at least three years after stopping estrogen therapy.[35,36] A recent report from the Nurses Health Study (a large, long term observational study of hormone use) suggests that women with at least one major risk factor for coronary heart disease (CHD) benefit more from estrogen therapy than women with no risk factors.[37] Among those at risk for CHD, a 49% decrease in death from all causes was seen, while women at little risk for heart disease had only an 11% reduction in mortality. Women who have diagnosed coronary heart disease and atherosclerosis may have an even more impressive 80% reduction in the risk of further disease or coronary death.[35] Evidence suggests that women with severe CHD are the most likely to benefit from estrogen therapy.[35,38] A recent International Consensus Conference of Postmenopausal Hormone Replacement Therapy and the Cardiovascular System stated that the cardiovascular benefits of estrogen replacement would likely outweigh any risks for most postmenopausal women. This group advocated the use of estrogen therapy for most women, based on the prevalence of cardiovascular disease and death.[38]

Estrogen has several effects which contribute to its cardioprotective action. The positive effect of estrogen on cholesterol levels—about a 15% decrease in LDL-cholesterol and a 15% increase in HDL-cholesterol—is thought to account for about 50% of its cardioprotective action.[39] Other cardioprotective mechanisms involve blood vessels and the heart: increased vasodilation, increased cardiac contractility, decreased accumulation of LDL-C in arteries and increased blood flow.[35]

The dose of estrogen used in most of the studies demonstrating a reduced risk of heart disease was 0.625-1.25 mg daily.[7] As a result, the dose currently recommended for cardioprotection is the same as that recommended for the prevention of osteoporosis—0.625 mg CEE/day. The estrogen delivery system and the addition of a progestin to the regimen both have a significant influence on the cardioprotective effects of estrogen. Transdermal estrogen does not appear to be as potent as oral estrogen in improving lipid levels. At this time, there are not enough data to demonstrate a cardioprotective effect from any non-oral estrogen formulation, and they are not recommended for the prevention of CHD.[37,38]

Progestins have an adverse effect on lipids—increasing LDL-C and decreasing HDL-C. There is some variation among progestins, with the more androgenic agents having a greater adverse lipid effect. While medroxyproges-terone acetate is the least androgenic of the synthetic progestins, it does decrease HDL-C in common therapeutic doses (e.g.,10 mg).[35] In women, HDL-C is more strongly related to heart disease than LDL-C. The concern with adding a progestin to estrogen therapy is that the cardioprotective effects might be diminished or lost. The recent PEPI trial, which compared the effect of estrogen alone and three estrogen-progestin regimens, showed that the addition of MPA reduced, but did not eliminate, the positive effect of estrogen on lipid levels. All hormone regimens decreased LDL-C and increased HDL-C to an extent that should be clinically beneficial.[40] The Nurses Health Study reported in 1996 that women taking estrogen and progestin had at least as great a reduction in heart disease risk as women taking estrogen alone.[36]

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— Resources — for HRT Information

North American Menopause Society (NAMS)
P.O. Box 94527, Cleveland OH 44101
Telephone: (216) 844-8748
http://www.menopause.org
(Answers written requests for information about menopause.)

American College of Obstetricians and Gynecologists
ACOG Resource Center
P.O. Box 96920, Washington DC 20090-6920
Telephone: (202) 484-3321
http://www.acog.com
(Send self-addressed, stamped, envelope for pamphlets about estrogen, menopause, or osteoporosis.)

American Association of Retired Persons (AARP)
Women's Initiative
601 East St., N.W., Washington DC 20049
Telephone: (800) 424-3410
(Has a free fact sheet about hormone replacement.)

Planned Parenthood Federation of America
810 Seventh Ave., New York NY 10019
http://www.ppfa.org/ppfa/menopub.html
(Has a booklet on menopause available for $3.)

National Osteoporosis Foundation
1150 17th St., Washington DC 20036
Telephone: (800) 223-9994 or (202) 223-2226
http://www.nof.org
(Has information for both professionals and consumers.)

Ovarian Cancer continued from page 23

should not be administered until the neutrophil count returns to >1000 cells/mm^3, platelets recover to >100,000 cells/mm3 and hemoglobin levels recover to 9 mg/dl. Neutropenia can be managed with granulocyte-colony stimulating factor (G-CSF) therapy, however G-CSF should not be given until 24 hours after the last topotecan dose to avoid prolongation of neutropenia. Studies with high dose topotecan with G-CSF revealed that concurrent therapy with G-CSF and topotecan resulted in severe bone marrow suppression. Administering G-CSF after the fifth day of therapy (day six) did not cause the same effect.[12] Topotecan can also cause hair loss and mild nausea and vomiting, usually not requiring serotonin type 3 receptor antagonist antiemetics (e.g., granisetron or ondansetron).

Docetaxel (Taxotere™), a new semisynthetic taxoid, has also been studied for the treatment of advanced ovarian cancer. It is currently approved by the FDA for the treatment of patients with advanced or metastatic breast cancer who have progressed during anthracycline-based therapy or have relapsed during anthracycline-based adjuvant therapy. A study was conducted of patients who received docetaxel for the treatment of advanced epithelial ovarian cancer with disease relapse or progression with platinum-based chemotherapy. Docetaxel was administered at a dose of 100 mg/m^2 as a 1 hour infusion every 3 weeks. The overall response rate was 24% with a median progression-free survival of four months. The median overall survival was 8.4 months. Toxicities most commonly associated with docetaxel are neutropenia of <2000 cells/mm^3, neurotoxicity, skin reactions, hypersensitivity reactions and fluid retention.[13] Pretreatment with oral corticosteroids such as dexamethasone 16 mg/day for five days, starting one day prior to docetaxel administration, reduces the severity and incidence of fluid retention and hypersensitivity reactions. Docetaxel appears to be effective in the treatment of platinum-refractory ovarian cancer patients.[13]

Other new chemotherapeutic agents which have shown potential for treatment of advanced ovarian cancer include liposomal doxorubicin (Doxil™) and gemcitabine (Gemzar™). Liposomal doxorubicin (Doxil™), an agent approved for the treatment of Kaposi's sarcoma, is being studied for use in advanced ovarian cancer. While the use of nonliposomal doxorubicin has not had a role as a second-line treatment for advanced ovarian cancer, the use of the liposomal doxorubicin has had favorable results. Gemcitabine (Gemzar™) is approved as a first-line treatment for patients with advanced or metastatic pancreatic cancer. Gemcitabine has also been studied for the treatment of advanced ovarian cancer. Response rates of 19%, with a median duration of response of 8.1 months and median progression-free survival time of 2.8 months, were demonstrated in previously platinum treated patients with advanced ovarian cancer.[14] The use of gemcitabine with platinum drugs is also being investigated for the treatment of advanced ovarian cancer.

Alternatives to Chemotherapy for Persistent/Recurrent Disease

In addition to chemotherapy for the treatment of recurrent or persistent disease, patients are sometimes treated with other methods, some of which are palliative therapies (i.e., therapies that relieve symptoms, but do not change the course of the underlying disease). A second debulking surgery is sometimes performed; however, this will only benefit a small, select group of patients.[4] Whole-abdomen radiotherapy has not been shown to improve survival in patients who have persistent residual disease after platinum chemotherapy.[7] However, radiation therapy can provide palliative therapy for patients with recurrent or metastatic ovarian cancer following first-line and second-line chemotherapy. The instillation of intraperitoneal (IP) chemotherapy is another approach sometimes used in patients with recurrent or persistent disease. The benefits of IP chemotherapy have not been clearly established. A recent study comparing IV cyclophosphamide plus either IV or IP cisplatin showed a significant survival advantage for the IP group, with less toxicity.[6] Patients with minimal tumors (<1 to 2 cm) after surgery are most likely to benefit from IP chemotherapy.[7] For all treatments, the risks of aggressive treatment, as well as the effect on the patients quality of life, should be considered. Often, for recurrent or persistent ovarian cancer, there is very little chance for a cure.

Summary

Because early stage ovarian cancer has a much better prognosis than advanced stage ovarian cancer, there is a great need for early diagnosis. Unfortunately, no effective screening method for the general public is available. The NIH currently recommends that women have an annual pelvic exam. Women at high risk for ovarian cancer should have a CA-125 test and transvaginal ultrasonography in addition to annual pelvic exams. Surgery is the primary treatment for ovarian cancer, with adjuvant chemotherapy, if necessary. Treatment with paclitaxel and platinum compounds is considered first-line therapy. With the newer chemotherapeutic agents becoming available, such as topotecan, there is renewed hope in the battle against ovarian cancer. ■

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Painful Menstruation continued from page 11

Generally, all the agents are effective when compared to a placebo, and no one particular NSAID appears to be more effective than another.[5]

Dosage & Administration

Most of the clinical trials involving NSAIDs and dysmenorrhea utilized individual doses and total 24-hour doses that were higher than the labeled nonprescription doses (see Table 2). It is likely that not all women will be adequately treated with the doses recommended on the OTC product labels. The dosing instructions for all the nonprescription NSAIDs mention that some patients may require more than a single tablet. The manufacturers of ibuprofen suggest that 2 tablets (or 400 mg) be taken if adequate relief is not obtained from one tablet (not to exceed 1200 mg in a 24-hour period). Both ketoprofen and naproxen manufacturers suggest doubling the initial dose to provide better symptom relief. An initial dose of naproxen sodium 440 mg can be followed by a 220 mg dose 12 hours later for a 24-hour total dose of 660 mg. Similarly, an initial dose of 25 mg of ketoprofen can be used with a maximum of 25 mg every 4-6 hours, or 75 mg in a 24-hour period.

For the treatment of dysmenorrhea, NSAIDs provide optimal pain relief when taken on a scheduled basis, rather than as-needed.[3,10] The patient should be instructed to take these drugs according to a scheduled regimen for the first several days of her menses when prostaglandin levels are highest. Scheduled dosing helps to prevent cramping, as well as to relieve pain. It is recommended that women vary the dose (according to package insert directions) as well as the type of NSAID for 3-6 cycles, if necessary, to determine which dose or agent will adequately relieve their symptoms.[1]

Side Effects & Drug Interactions

Side effects from short-term NSAID therapy are mild. The most common side effect of all NSAIDs is gastrointestinal distress (e.g., upset stomach, nausea, abdominal cramps), which occurs in 3-9% of patients. Other side effects include constipation, diarrhea, gas, headache, dizziness, nervousness, ringing in the ears, and fluid retention. If a woman experiences side effects with a particular NSAID, switching to another NSAID may solve the problem.

NSAIDs have several important drug-drug interactions. They can decrease the effectiveness of antihypertensive agents, including ACE inhibitors, beta blockers, alpha blockers, and diuretics. NSAIDs can also increase the potential for toxicity from anticoagulants, lithium, and high dose methotrexate.[11]

Alternative Treatment

Women with dysmenorrhea who do not respond to nonprescription therapy should be referred to a clinician. Other treatment options include an increased dose of the nonprescription NSAID, a trial with one of the prescription NSAIDs, or the use of an oral contraceptive. About 80-90% of women with primary dysmenorrhea will experience adequate symptom control with the use of an NSAID, an oral contraceptive, or the combination.[4] Treatment options for more difficult cases include therapy with a calcium channel blocker, transcutaneous electrical nerve stimulation (TENS), and uterine surgery.

Summary

Correct administration of nonprescription products and general knowledge about the condition can lead to effective self-management of dysmenorrhea. However, there are women who are not appropriate candidates for nonprescription therapy and others who will not be adequately treated with OTC drugs. Appropriate referral to other health care providers is an important aspect of managing dysmenorrhea. Pharmacists who take an active role in educating women about the treatment of dysmenorrhea will make a substantial contribution to the health of their patients.

Consumer Counseling Information

- The OTC NSAIDs available for the treatment of dysmenorrhea are equally effective. Selection can be based on previous experience with a product, preference, and cost. NSAIDs vary in the number of daily doses required. In addition, some drugs are available as less expensive generic products.
- Women should not self-treat with NSAIDs if they have a history of allergy to aspirin or any NSAID, a history of GI disease (e.g., peptic ulcer disease, gastroesophageal reflux disease, ulcerative colitis) or a history of bleeding disorders. Women with symptoms that are not typical for primary dysmenorrhea and those who do not respond to NSAIDs should be evaluated by a physician.
- When starting NSAIDs treatment, begin therapy at the onset of menses (rather than prior to menses) to assure that pregnancy is not indicated. The usual length of therapy is 2-3 days, which is consistent with the general period of pain and cramping.
- Side effects of NSAIDs are limited, since use is continued for just a few days. Gastrointestinal effects (upset stomach, abdominal discomfort, cramps) are the most common. These can be minimized by taking each dose with food or a full glass of liquid and avoiding caffeine, alcohol, and aspirin. Other side effects vary among the OTC drugs; patients may benefit by trying a different NSAID.

* A woman should use nonprescription NSAIDs for 3-6 menstrual cycles, varying the dose and the specific drug, to determine if adequate relief can be achieved and which product and dose is best for her.

* Not all women will respond to the nonprescription NSAID products. Patients should be informed about prescription options such as higher doses of the OTC drugs, different NSAIDs, and oral contraceptives. ■

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Breast Cancer continued from page 19

Docetaxel is the second taxane to be developed. A partial response rate of 41% and a complete response (no detection of tumor) rate of 2% have been noted for this drug, with a median duration of response of 6 months and a median time to progression of 4 months. Median survival time was 10 months.[10]

The recommended dosage for docetaxel is 60-100 mg/m^2 given over 1 hour every three weeks. Longer infusion times have caused mucositis (mouth sores) and more severe neutropenia (lowering of white blood cells). Neutropenic nadirs usually occur on day 8, with recovery by day 21.

Side effects of docetaxel include grade 4, or severe, neutropenia (75-90% of patients); febrile neutropenia (0-22%); grade 1 to 3, or mild to moderate, hair loss (80%); and fluid retention (40%) seen as weight gain, edema or pleural effusions. Fluid retention is related to increased capillary permeability, and is treated with dexamethasone (8 mg orally twice a day), beginning the day before and continuing 3 days after the infusion of docetaxel. Patients with neutrophil counts of less than 500 cells/mm^3 for more than one week or severe peripheral neuropathy should have subsequent doses decreased to 75-55 mg/m^2, or the treatment discontinued.

Vinorelbine, a vinca alkaloid, is a new addition that offers the potential of less neurotoxicity than vincristine or vinblastine. Response rates in patients without prior therapy are 40-60%, whereas response rates in patients with prior therapy are 20-30%. Vinorelbine is given as an IV infusion into a large, central vein. However, improper administration (outside the central vein) may result in local tissue damage.

The topoisomerase I inhibitors topotecan and irinotecan (CPT 11) have shown promise in the treatment of metastatic breast cancer. These agents, although not FDA-approved for this use, have had encouraging results in phase I trials.

TABLE 8

New Second Line Agents in Breast Cancer

Class	Drug	Dose (mg/m^2)
Taxanes	Paclitaxel	135-250 I.V. over 3 hours
	Docetaxel	60 - 100 I.V. over 1 hour
Vinca Alkaloid	Vinorelbine*	30 Slow I.V.P.
Topoisomerase I Inhibitor	#Topotecan	1.5 I.V. over 30 min. X 5 days
	#Irinotecan (CPT 11)	125 I.V. over 90 min

*Unlabeled use

Not FDA approved for breast cancer

A Look To The Future

The development of new and effective cytotoxic agents over the last three years and the formulation of original and exciting treatment approaches hold promise in the fight against primary and metastatic breast cancer. There is a growing understanding of the hormonal regulation of breast cancer cell proliferation, which has led to new avenues of research, particularly toward the ability to bind monoclonal antibodies to specific receptors. These receptors play an important role in the development and growth of mammary carcinoma by producing diffusible products that enhance the growth of breast cancer cells. This new understanding of growth regulation may play an important role in the development of therapies that target tumor expansion by interfering specifically with the factors that control their growth. ■

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Coronary Artery Disease continued from page 15

does for men. Treating an acute MI with thrombolytic therapy has been shown to be beneficial for women in terms of survival. Unfortunately, the benefit is not as great as it is for men, and serious bleeding complications are more frequent in women.

Percutaneous transluminal coronary angioplasty (PTCA) is a procedure that opens coronary vessels that have narrowed as a result of CAD. Women initially have less symptomatic and angiographic success and higher in-hospital death rates than men. This may be related to older age and the presence of more concurrent diseases or medical conditions. However, the long-term outcome for women is actually better, and restenosis (or renarrowing of the vessels) is less likely in women. Women have a significantly higher rate of angiographic and clinical complications with coronary atherectomy and following the insertion of devices such as stents. This may be due in part to the smaller coronary vessel size in older women.

Women who undergo coronary artery bypass grafting surgery (CABG) have roughly twice the postop death rate as men, but similar 5- and 10-year survival rates. There appear to be several reasons for this situation. Women are more likely to undergo emergency surgery, have more advanced disease, and are at a later, more symptomatic stage of disease when they undergo a CABG procedure. Smaller blood vessels in women may reduce the opportunity to obtain complete revascularization. Women referred for CABG are more likely to have diabetes, hypertension, and congestive heart failure and are less likely to have had an MI. Women are more likely to suffer from depression after MI and are less likely to be referred to cardiac rehabilitation programs than men.

Risk factor modification is very important in the management of CAD in women. As mentioned above, smoking cessation can lower the risk of CAD, as well as lower the risk of a second MI more than any other risk factor modification. Weight reduction and probably glycemic control in women with diabetes are important for lowering the risk of CAD. Controlling hypertension and hyperlipidemia, and following a low-fat diet and a regular exercise program should be encouraged.

Conclusion

Coronary artery disease is the leading cause of death in US women. It is a rare event in premenopausal women, but 15 to 20 years after menopause the incidence is equal among women and men. Risk factors for CAD in women include advanced age, smoking, diabetes, hypertension, family history, obesity, elevated cholesterol, and being postmenopausal without hormone replacement therapy. Unfortunately, the diagnosis can be difficult, because women often present with nonclassic angina, and diagnostic tests aren't as sensitive or specific in women. Medical treatment of CAD in women is similar to that in men, with the exception of HRT. Forms of interventional treatment such as angioplasty and surgery have higher postop complications in women than in men, but these treatments can be equally effective in the long run. Finally, risk factor modification should be attempted at all stages of treatment. ■

Osteoporosis continued from page 33

acts directly on osteoclasts to inhibit bone resorption. Calcitonin has been used in diseases of calcium metabolism characterized by increased bone turnover, including osteoporosis and Paget's disease. Salmon-calcitonin is a synthetic polypeptide that has similar activity to mammalian calcitonin, but is more potent and has a longer duration of action.

Intranasal salmon-calcitonin is a new dosage form that is FDA-approved for the treatment of postmenopausal osteoporosis. Until recently, calcitonin was available only for subcutaneous or intramuscular injection. The intranasal formulation provides similar efficacy to that of injectable calcitonin in the prevention of bone loss. It is a more acceptable alternative for women who are unable to tolerate injectable calcitonin, HRT, or alendronate.

Intranasal calcitonin is dosed as one spray per day (which delivers 200 IU of calcitonin). Most adverse effects of the intranasal formulation are local (mild rhinitis, or runny nose). Nasal irritation can be avoided by alternating nostrils each day. Treatment failure may occur in patients with allergic rhinitis. Calcitonin therapy is contraindicated in patients with hypocalcemia.

In a randomized, double-blind, placebo-controlled trial, Overgaard et al. showed that nasal calcitonin provides a dose-dependent increase in spinal BMD (3%), and a reduction in vertebral fracture risk by two-thirds in elderly women (68-72 years old) with osteoporosis.11 In addition, calcitonin provides a potent analgesic effect in individuals who have osteoporosis with the presence of a fracture. The mechanism for this analgesic effect is unclear.[12]

Fluoride

Fluoride decreases bone resorption, and unlike other antiresorptive agents, stimulates osteoblast proliferation to increase bone formation. However, fluoride use is controversial; there are concerns regarding both its efficacy and its risks. Histological studies show that new bone formed in response to fluoride may be poor in quality, have increased fragility, and an increased risk of fracture.[13] If fluoride is taken without high dose calcium supplementation, substantial calcium content can be lost from the skeleton. A four-year study of postmenopausal women with osteoporosis and vertebral fractures by Riggs et al. demonstrated that sodium fluoride in daily doses of 75 mg increased spinal BMD but also decreased bone strength.[14] Presently, fluoride is not FDA-approved for use in osteoporosis due to the above stated concerns despite its wide use in Europe.

Adverse effects, which are primarily gastrointestinal, are common. Nausea, vomiting, upset stomach, and gastrointestinal bleeding have all been reported. With immediate release products, lower extremity pain involving the feet, ankles, and legs has been reported. It is not clear if these effects are related to fluoride or result from stress fractures. Long-acting or slow release products may decrease the gastrointestinal effects.

Conclusions

Osteoporosis is a disease that is best managed with preventive measures. Maximizing peak bone mass with weight-bearing exercise and adequate intake of calcium and vitamin D are key preventive measures, whether drug therapy to prevent bone loss is initiated or not. Questions which must still be answered include who should have bone mineral density screening, and what is the optimum age for beginning drug therapy?

There are not sufficient data to show that treating everyone for fracture prevention is cost-effective; however, individuals with low bone mineral density and a history of bone fracture are at the highest risk for future fractures and should be treated. HRT remains the standard therapy for prevention and treatment of postmenopausal osteoporosis. Other promising alternatives include alendronate and intranasal calcitonin, and raloxifene. In the future, measures to assess drug efficacy may include periodic BMD measurements as these procedures become more affordable and widely available. ■

TABLE 2

***Possible Risk Factors for Candida Vulvovaginitis*[5,9,10]**

Broad-spectrum antibiotics	Not all women are affected: there may be a subgroup of patients who develop increased vaginal candida.
Estrogen-containing oral contraceptives	Recent studies do not show an increased risk with low-dose (30-35 mcg) contraceptives.
Corticosteroids, Antineoplastics, Immunosuppressants	Can decrease host immune defenses and allow candida to proliferate.
Pregnancy	Studies are inconclusive; some women may be affected.
Diabetes mellitus	Risk is increased, particularly with poor control of blood glucose.
Immunocompromised patients	Increased risk in organ transplant recipients and HIV/AIDS patients.
Diet	Risk may increase with foods that elevate urinary sugar (e.g., milk, yogurt, cottage cheese). Conversely, daily consumption of active culture yogurt may protect against infection by controlling quantity of candida in the body[6]
Tight clothing/ pantyhose	While often implicated, studies do not support an increased risk.
Frequency of sexual intercourse	May facilitate entry of candida to vagina and may cause minor vaginal trauma, increasing risk.
Sexual partners	There is no evidence that treatment of male partners prevents recurrence of vaginal candida infections in women.

Yeast Infections continued from page 13

or non-albicans strain of candida). Other patients who should not self-diagnose or self-treat include pregnant women, girls under the age of 12 years, patients with concurrent symptoms such as fever or abdominal pain, patients taking immunosuppressant drugs, and those with medical conditions (e.g., diabetes mellitus, HIV infection) which might predispose them to candida infections.

Vaginal Antifungal Therapy

There are currently four nonprescription imidazole vaginal antifungal drugs on the market: butoconazole, clotrimazole, miconazole, and tioconazole. Topical imidazole antifungals are the recommended initial therapy for candida vulvovaginitis. All of the prescription and nonprescription imidazole products are very effective and are regarded as equally effective, with clinical cure rates in the range of 85-90%.[7]

Therapy with vaginal antifungals involves once a day application, usually at bedtime. The duration of therapy varies; tioconazole offers one-day therapy, butoconazole has a three-day regimen, while clotrimazole and miconazole have both a three-day and a seven-day regimen. These regimens are equally effective for women with uncomplicated infections. While nonprescription products are available as suppositories, creams, or vaginal tablets, there is no evidence that one formulation is more effective than another.[10] Patient preference often determines which type of product is used. A cream or the combined use of a cream and a vaginal suppository or tablet is recommended for women with vulvar symptoms so the antifungal can be applied both externally and vaginally (see Table 1 for dosage regimens).

Mechanism of Action

The imidazoles have several effects which damage fungal cells. They inhibit the synthesis of essential fungal sterols, resulting in structural damage to the cell membrane and loss of membrane function. Imidazoles also inhibit enzyme activity, causing toxic concentrations of hydrogen peroxide to accumulate. This leads to deterioration of cell organelles and cell necrosis and inhibits the transformation of fungal cells into an invasive form.[11]

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Side Effects

Topically applied imidazoles are absorbed to a limited extent (1-10%),[2,11,12] and side effects are minimal. About 7% of patients experience some local burning, itching, or irritation, usually with the first dose of the vaginal preparation.[13,14] Local side effects may be more common with tioconazole. Headache, abdominal cramps, urinary frequency, abnormal sensations (e.g., burning, tingling), runny nose, fever and chills, and penile irritation during intercourse are possible but rarely occur.[13] There are no clinically significant drug interactions with these agents, and the only absolute contraindication to their use is an allergy to the products.

Patient Response & Follow-up

Monitoring for effectiveness is based on patient symptoms. Relief of symptoms can occur within hours of the initial dose, although this is not indicative of cure. It is important for women to finish the recommended course of therapy because many recurrences of candida vulvovaginitis are thought to result from incomplete treatment.[14] Antifungal activity persists longer than the short courses of therapy (1 or 3 days), and resolution of symptoms may occur several days after treatment. If a woman has not experienced any improvement in symptoms within three days after beginning therapy, or if symptoms persist after a week, she should be referred for clinician evaluation. A pelvic exam and an examination of vaginal secretions should be done to confirm a diagnosis, and rule out pathogens other than candida albicans. It is estimated that 15-20% of vaginal infections are mixed infections.[10] A woman should also be referred for further evaluation if vaginal symptoms recur within two months of nonprescription therapy.

Use During Pregnancy

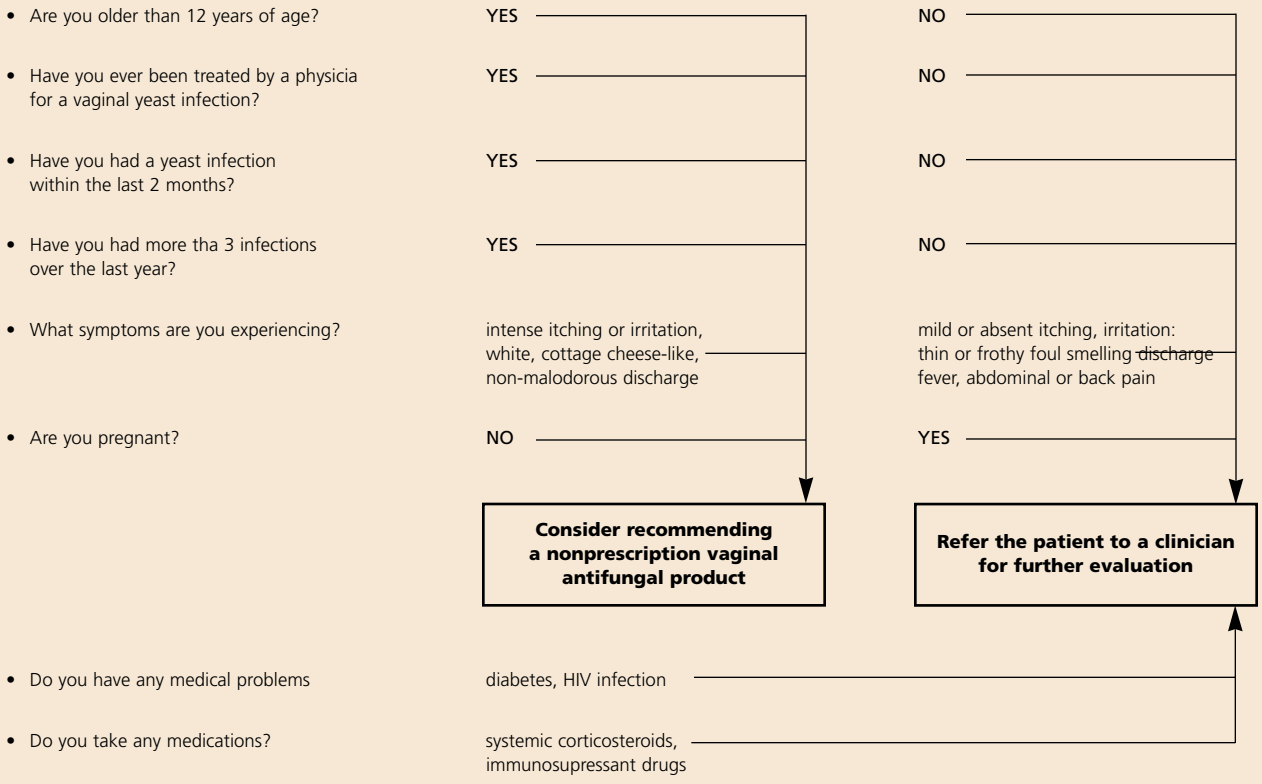
The nonprescription antifungals are not recommended for use by pregnant women. However, under the direction of a physician, topically applied imidazole antifungal agents are the drugs of choice during pregnancy because there is little systemic absorption. Candida vulvovaginitis tends to be more difficult to cure during pregnancy. For this reason, the prescribed duration of treatment is usually longer (e.g., 1 or 2 weeks for clotrimazole or miconazole and 6 days for butoconazole).[10,14] Most clinicians recommend that the vaginal antifungals be used only during the second and third trimesters.[13,15] However, clinical trials, some of which included women in the first trimester of pregnancy, have not shown any adverse effects on the baby or the mother.[16] It is not known whether these agents are excreted in breast milk, but it is unlikely that clinically significant concentrations occur. Adverse effects in human infants have not been documented.

Other Treatment Options

When nonprescription antifungal therapy is ineffective, a physician may recommend a second course of vaginal therapy, a longer course of therapy (e.g., 2-3 weeks), the use of boric acid capsules intravaginally, or terconazole therapy

TABLE 3

Questions for Women Who May Have a Vaginal Yeast Infection



Questions for guide product selection:
What antifungal drug did you use last time you had a yeast infection? Was it effective? Any side effects or problems?
Do you have a preference for a cream, vaginal tablet or suppository? Do you have itching or irritation outside the vagina?

Yeast Infections continued from page 43

(this triazole antifungal is more effective against non-albicans species of candida).[13,17,18] Intravaginal boric acid has been shown to be quite effective for chronic non-candida albicans mycotic vaginal infections with mycologic cure rates of 77-85%. The oral antifungals—fluconazole, itraconazole, and ketoconazole—have also been studied for the treatment of candida vulvovaginitis, but only fluconazole (Diflucan™) is currently FDA approved for this indication.

The oral antifungals are comparable in efficacy to the topical agents and are promoted as compliance-enhancing because of convenience and patient preference for oral therapy.[13,15] However, some clinicians feel oral therapy should be reserved for severe, recurrent cases of candida vulvovaginitis because the risks of oral therapy outweigh the benefits for uncomplicated infections.[13] Disadvantages of the oral agents include a greater incidence of side effects, increased risk of serious adverse drug effects, and a potential for drug interactions. Oral therapy can also be more expensive, due to greater cost of the medication and the need for physician visits and laboratory monitoring.

Recurrent candida vulvovaginitis is difficult to treat and often requires long-term (6 months) suppressive therapy. The vaginal imidazole antifungals are often administered once or twice weekly as suppression therapy.[13,15] Oral agents may also be used; 100 mg ketoconazole daily or 150 mg fluconazole once monthly are two common regimens.[13,15]

Facts for Consumers Regarding Vaginal Antifungals:

- It is important to complete the full course of therapy. Symptoms may disappear quickly, but this does not mean the infection is cured.
- If symptoms do not improve within three days after beginning of therapy or persist after a week, it is time to see a physician for evaluation.
- If symptoms recur within two months of therapy, evaluation by a physician is necessary. Recurrent infection may be an early sign of a serious medical problem such as diabetes or HIV infection.
- The OTC antifungal agents available for the treatment of yeast infections are considered equally effective. Selection can be based on previous experience with a product, preference, and cost.

Consumer Counseling Tips

Advise women to consult a physician before using the OTC vaginal antifungal products if it is their first experience with vaginal itch or discomfort.

Self-treatment is not appropriate during pregnancy, in a woman with diabetes, or if the woman has symptoms that indicate a systemic infection (e.g., fever, abdominal or back pain). Women taking systemic corticosteroids or anticancer medications should not self-treat for candida vulvovaginitis.

If menses begins during the course of therapy with a vaginal antifungal, therapy should be continued. Instruct women not to use tampons while using a vaginal antifungal, as they can absorb the medication. If a woman prefers not to use these products during menses, treatment can be postponed until afterwards.

Patients should be advised to abstain from sexual intercourse during therapy and instructed that vaginal antifungals may decrease the effectiveness of condoms, diaphragms, and cervical caps. The use of condoms and diaphragms should be avoided for 72 hours after vaginal insertion of tioconazole. Concurrent use of a vaginal antifungal and a contraceptive foam (or cream) can result in decreased effectiveness of both products.

Side effects from vaginal antifungals are uncommon. Some women experience transient burning, irritation, or itching when therapy is started. There may be some leakage of the product from the vagina, and it is suggested that women use sanitary napkins during therapy. ■

Depression continued from page 30

some extent, on the length and type of antidepressant therapy, speed of dosage taper, and provider awareness. It is important for health care providers to recognize, prevent, and manage antidepressant withdrawal symptoms which may include flu-like malaise, subtle mental symptoms, GI effects, changes in sleep and dreaming, sensations such as burning or tingling, and cholinergic symptoms.

Other Treatments for Depression

Nondrug therapies—Psychotherapy is an important component in the treatment of depression, and it may be used alone or in combination with antidepressants. Many forms of psychotherapy are used; short-term therapy is common and usually lasts 10-20 weeks. Most health care organizations offer an array of educational classes in such subjects as relaxation, mood management, depression, and mind/body medicine. Light therapy has been used in cases of seasonal depression. Electroconvulsive therapy (ECT) is usually reserved for refractory or geriatric depression, although response rates are high and the risks are low with modern administration methods.

Supplemental medications—Psychotropics such as lithium, carbamazepine, or valproic acid may be used with antidepressants in bipolar mood disorders. Antidepressants may actually precipitate mania in individuals who have bipolar illness. Thyroid hormone has been combined with antidepressants to enhance the antidepressant effect. Stimulants such as dextroamphetamine or methylphenidate (which has less cardiovascular effect than dextroamphetamine) are used primarily in elderly, apathetic, or medically ill individuals. Antipsychotics are used in conjunction with antidepressants in cases of depression with psychotic features.

Conclusion

Whether in a retail, clinic, or hospital setting, the pharmacist has an important role in the treatment of depression that can directly impact the patient's quality of life. Pharmacists can help ensure that depression is recognized and treated early, appropriately, and successfully in both females and males. An important aspect of providing pharmaceutical care to patients with depression is encouraging patients to seek help and follow through on therapy for this highly treatable condition. Pharmacists should work collaboratively with other health care professionals and:

- understand the diagnosis of depression and recognize the symptoms;
- contribute to an appropriate individualized drug choice;
- help ensure an adequate drug trial—assess the drug, dose and duration of therapy;
- promote patient compliance;
- provide patient and family education regarding expectations and therapeutic goals;
- monitor for effectiveness, side effects and drug interactions;
- be aware of and learn about new research and new drugs; and
- document their impact on the delivery of health care in these areas: patient-focused care, optimal drug therapy, continuity of care, and positive patient outcomes. ■

Contraception continued from page 9

to the use of hormonal agents include current thromboembolic disorders and a history of hormone-sensitive tumors. The package inserts contain patient contraindications for use.

Hormonal contraceptive formulations include a progestin, with or without an estrogen. Progestins are the predominant pharmacologically active component of all hormonal methods. Progestins inhibit ovulation by inhibiting luteinizing hormone which produces changes in cervical mucus that are hostile to sperm, and by altering the endometrium, which makes implantation unlikely.[4] The estrogen component serves to stabilize the endometrium (which prevents irregular bleeding), suppress ovulation by inhibiting follicle stimulating hormone, and potentiate the effects of progestin.

Estrogen-related side effects include nausea, breast tenderness, fluid retention, and cyclic weight changes. Estrogens may also have adverse effects on the coagulation system which are related to thromboembolic complications.[1,3] Progestin related side effects include weight gain, acne, depression, and possibly changes in the lipid profile. Progestins may also produce a thinning of the endometrium, which results in scanty withdrawal bleeding or amenorrhea.

Oral Contraceptives

Oral contraceptives are the most widely utilized method of contraception in the United States. Oral contraceptives provide reliable, reversible, and easy-to-use contraception, with significant health benefits to users and relatively minor and uncommon side effects. Noncontraceptive health benefits include reduction in the risk of endometrial cancer and ovarian cancer, a reduced risk of ectopic pregnancy, improved cycle control, reduced anemia from heavy menses, a reduction in pelvic inflammatory disease, a decreased risk of rheumatoid arthritis, and increased bone density. Despite proven health benefits, many misconceptions and concerns regarding the safety and risks of oral contraceptives remain; education continues to be important in removing confusion and relieving concerns.

Combination oral contraceptives contain both an estrogen and a progestin and are prescribed for 21 consecutive days followed by a seven-day hormone-free interval. Formulations can be monophasic, biphasic, or triphasic. Monophasic regimens provide fixed doses of estrogen and progestin for 21 days. Biphasic formulations provide a fixed estrogen dose and an increased dose of progestin for the last 11 days of the cycle. Triphasic formulations, which have been widely utilized over the past five years, provide increasing doses of progestin every seven days, and either a fixed or increasing dose of estrogen, throughout the cycle.

The initial oral contraceptive selected should be the lowest estrogen dose formulation which effectively prevents pregnancy. Nearly all of the products available today contain ethinyl estradiol as the estrogen component. In 1996, approximately 98% of all oral contraceptive prescriptions were for products containing 35 mcg or less of estrogen. An increase in spotting or breakthrough bleeding may occur with lower dose formulations, usually during the first three cycles of contraceptive use. Patients should be reassured that the bleeding is temporary and that spotting does not indicate decreased efficacy. An increased risk of thromboembolic complications corresponds with increased estrogen doses. Estrogen doses above 50 mcg of ethinyl estradiol induce changes in the coagulation and fibrolytic system. It is not clear if these changes occur with doses of 20 mcg ethinyl estradiol.[1,10] Currently, the recommended combination oral contraceptives are those containing 35 mcg of estrogen or less.

There are several progestins currently approved for use in oral contraceptives and more products are in development. Little conclusive evidence exists to demonstrate that any one progestin is more effective than the others. The newer or second generation progestins are reported to have beneficial effects on the blood lipid profile. The long term benefits of these lipid effects will not be known for several years. Patients who are sensitive to progestin may benefit from products with lower total progestin doses, including multiphasic preparations.

Combination Oral Contraceptives and Cancer

The risk of ovarian cancer in users and past users of combination oral contraceptives (COC) is reduced by approximately 40%. The protective effect from COC increases with increased duration of use, and is thought to result from inhibition of ovulation. Protection persists for as long as fifteen or more years after discontinuation of COC use.10 A reduction in the incidence of endometrial cancer has also been reported in users and past users of COC. Women who used COC for at least 12 months have a reduction of 40% in the incidence of endometrial cancer. As with ovarian cancer, the protection persists for up to 15 years after discontinuing COC use. Pelvic inflammatory disease (PID) is a significant factor in infertility in the United States. The use of COC decreases the risk of hospitalization from PID significantly.[10]

The incidence of breast cancer may be slightly increased in users of COC; however, this remains controversial. COC are protective against benign breast disease but not breast cancer. Data collection is still under way to better define the role of COC in breast cancer risk. Patients should be reassured that the increased risk of breast cancer from COC is small.[5] An increased risk of thromboembolism in users of COC was identified many years ago. The risk was associated with higher doses of estrogens, and identification of this risk contributed to the lowering of estrogen doses in COC. An increased risk of cervical cancer in COC users has also been reported which appears to be linked to the use of COC for six or more years. However, the increased risk is small, and the studies identifying this risk did not control adequately for variables such as smoking or multiple sexual partners, which are independent risk factors for cervical cancer. Women using COC should be advised to have regular PAP screening for cervical cancer.[5]

Oral Contraceptives and Acne

Acne is generally improved in women taking any formulation of COC, although some patients using androgenic progestins may experience an increase in acne. However, such increases are less common.

Patient Counseling and Combination Oral Contraceptives

Patient counseling for women who use combination oral contraceptives is important both to clarify instructions for administration and to inform patients of side effects. A back-up method of contraception should be discussed and provided with the initial prescription. Instructions for missed pills should also be discussed (see Table 2). Common side effects, including nausea, spotting, and potentially serious effects (see ACHES, Figure 1) should be reviewed. Patients with nausea may find it helpful to take the dose at bedtime. Women should be reassured that nausea and spotting decrease considerably after the first 3 cycles of use. Because many women believe that a periodic rest from oral contraceptives is beneficial, they should be advised that there is no reason to discontinue COC for a rest. Women who do discontinue oral contraceptives for a rest should be advised that substituting a less effective form of contraception may increase their risk for pregnancy. Again, education is a key to effective use of oral contraception.

Progestin-Only Oral Contraceptive

Progestin-only oral contraceptives are an attractive option for women unable to tolerate estrogen and those who are breastfeeding. The efficacy of progestin-only pills is lower than that of combination oral contraceptives. Also, because of the relatively low doses of progestin-only pills, patients must strictly adhere to the daily regimen, taking the doses as close to every 24 hours as possible: patients who miss pills or take pills on an irregular schedule are more likely to ovulate and become pregnant.

The initial cycle of progestin-only pills should be started on the first day of menses. Patients should be instructed to take one pill every day continuously. There are no pill-free days in a progestin-only regimen.

Irregular bleeding is common in progestin-only pill regimens and is a major reason for discontinuation. Many women experience short, irregularly spaced cycles or amenorrhea, and they are often concerned about the possibility of pregnancy in the absence of regular cycles. It may be reassuring to the patient to keep home pregnancy tests available in the home.

Patient counseling for progestin-only oral contraceptives should include the importance of taking the pills at exactly the same time every day. Patients should be educated about the possibility of spotting and irregular menstrual cycles. Back-up contraceptive regimens should be discussed and a back-up contraceptive dispensed to the patient.

Depo-Provera™ Injection

Introduced in 1992 in the United States, Depo-Provera™ (depo-medroxyprogesterone acetate, DMPA) is a highly effective, long-acting progestin-only method of contraception. The efficacy of DMPA is high because, unlike other progestin-only methods of contraception, the dose of progestin is high enough to suppress ovulation reliably. The injection is effective for 12 weeks; therefore patient compliance is high.

DMPA injections should be initiated during menses or within the first five days of the cycle and repeated every 12 weeks. Contraceptive activity is immediate if given during menses, and no back-up method is required. If the first injection is not given within the first five days of the cycle, a pregnancy test should be done to exclude pregnancy and a back-up method used for the first two weeks.

Good candidates for DMPA include women who have difficulty complying with oral regimens, women seeking long-lasting contraception, women taking medication for seizure disorders, women intolerant of estrogens, breastfeeding women, and possibly women with a history of thromboembolism. Noncontraceptive benefits of DMPA include lack of an effect on lactation, decreased risk of endometrial cancer, reduced menstrual flow, reduced risk of PID, reduced risk of endometriosis, and fewer ectopic pregnancies.

Problems with DMPA include a high incidence of irregular bleeding and amenorrhea. However, irregular bleeding tends to stabilize with continued use, and many patients experience complete amenorrhea (80%) after one year. A delay of six to nine months in the return to fertility is possible following discontinuation of DMPA injections. A reduction in bone density has also been reported with the use of DMPA, but the reduction is mild and reversible upon discontinuation. Patient education should include information regarding irregular bleeding and the delay in return to fertility.

Norplant™ System

The Norplant™ contraceptive system consists of long-acting progestin (levonorgestrel) containing rods that are implanted subdermally. The Norplant™ system is highly effective, rapidly reversible, and provides protection against pregnancy for five years. Levels of levonorgestrel are sufficient to prevent pregnancy within 24 hours of insertion and fall to ineffective levels within 24 hours of removal.

A significant number of patients using Norplant™ report menstrual irregularities. Irregular spotting and bleeding are common reasons for removal of Norplant systems within the first year of use. Bleeding irregularities tend to stabilize after the first year of use.

Good candidates for Norplant™ systems include breastfeeding women, women who have completed childbearing but do not want sterilization, women seeking long-term protection from pregnancy, women who cannot tolerate estrogens, and women who have difficulty complying with other methods of contraception. Patients who are properly educated about this method are more likely to be satisfied and experience safe, effective, long-lasting contraception.

Barrier Methods

The use of barrier methods for contraception dates from at least the earliest historical times of man. Currently, barrier methods of contraception are less popular than hormonal methods. The use of condoms for contraception has declined, but condom use for prevention of sexually transmitted diseases has increased dramatically in the last two decades and largely because of AIDS.[1]

Barrier contraceptives mechanically block the access of sperm to the egg. Barrier methods are most effective when combined with a spermicidal agent. Unlike hormonal contraceptives, barrier methods are free of systemic effects. Barrier methods are temporary and used during or in anticipation of intercourse and require consent and proper use to insure efficacy.

Diaphragms are latex rubber devices inserted into the vagina and positioned over the cervical opening. Diaphragms must be fitted by a health care provider, and patients should be refitted after childbirth. A diaphragm can be inserted up to six hours before intercourse, but should not be removed until six hours after intercourse. Repeated sexual intercourse requires the application of additional spermicide to the vagina without removing the diaphragm. (However, some patients may experience a burning or irritation from the spermicide.) There may be an increase in urinary tract infections when using diaphragms, and to minimize the risk of urinary infections, women should be encouraged to void after intercourse. For recurrent cases, a post-coital antibiotic regimen may be prescribed.

Condoms are an inexpensive, temporary barrier contraceptive which may provide protection from some sexually transmitted diseases. The contraceptive efficacy of condoms varies significantly due to improper or inconsistent use and the quality of material used. Male condoms are more effective than the female condom. Male condoms are available in latex, polyurethane, and natural skin varieties. Latex and polyurethane condoms provide protection from some sexually transmitted diseases, while natural products do not. Male condoms may include a lubricant or a spermicide. The female condom is polyurethane and does not require application of a spermicide. Condoms are a good back-up method of contraception. Patients who use condoms for contraception should

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be counseled regarding proper use and receive information about post-coital contraception regimens in the event of breakage or noncompliance.

Spermicidal Agents

Spermicidal agents are available as creams, foams, jellies, films, and suppositories. The most common active ingredient is nonoxynol-9, which is thought to exert its contraceptive effect by destroying the cell wall of sperm. For optimal protection, spermicidal agents must fully disperse in the vagina, cover the cervix, and be applied within the time guidelines provided in the product literature. Additional spermicide must be used for repeated sexual intercourse. Spermicidal agents are a readily available, inexpensive, reversible, nonprescription method of contraception. The efficacy is lower in comparison to hormonal products or barriers. The combination of a male condom and a spermicidal agent may be equal to that of COC. Spermicides are a good choice for back-up contraception. Local irritation and allergic reactions may be experienced by either partner.

Future Methods

The future offers additional methods of contraceptive hormone delivery, including vaginal rings, better tolerated injections, biodegradable implants, and lower dose oral contraceptive formulations.

Conclusion

Contraceptive methods in the United States have improved in safety, efficacy, and variety over the past several decades. The variety of contraceptive choices has improved the quality of life for women. Patient education and counseling are essential to ensure the efficacy of currently available methods and to help patients select a method which best suits their needs. Pharmacists not only are able to provide the contraceptives, but are also in an ideal position to provide the education and support needed by patients who are making choices about contraceptive methods.

As the results of long-term studies which answer questions about the risk of breast cancer and the noncontraceptive benefits of hormonal products become available, the best use of these products will become clearer. Improved availability of contraceptives and better patient education may result in a decrease in the unplanned pregnancy rate in the United States. Programs designed to reduce teenage pregnancy and increase contraceptive use in this age group may also reduce the rates of unplanned pregnancies. ■

Hormone Replacement continued from page 37

Estrogen therapy is one of several effective methods recommended to reduce the risk for heart disease. Nonhormonal approaches generally address risk factors such as high blood pressure, undesirable cholesterol levels, cigarette smoking, and obesity. Both drug (antihypertensives, cholesterol lowering agents) and nondrug (dietary changes, exercise) measures can be used, but compliance may be a problem.

Contraindications & Adverse Effects

Contraindications

The potential risks of HRT can range from relatively minor to grave, and based on their medical histories and/or conditions, some women should not use it. The absolute contraindications to postmenopausal estrogen therapy are: estrogen-related cancers (uterine, breast), undiagnosed abnormal vaginal bleeding, active liver disease or chronic severe liver dysfunction, active thrombophlebitis or thromboembolic disorder, malignant melanoma, and prior complications from estrogen therapy (e.g., cholestatic jaundice, migraine headache).[41,42] Additionally, there are clinical situations where the risks from the therapy might outweigh its potential benefits. These include an increased risk for thromboembolic disease (estrogen increases the risk for thromboembolism),[43,44] a history of gallstones (estrogen reduces the solubility of cholesterol),[45] conditions aggravated by fluid retention (e.g., congestive heart failure, seizure disorders, asthma),[45,46] and active endometriosis and benign uterine tumors (estrogen use inhibits postmenopausal resolution of these conditions).[41]

HRT has generally been avoided in women with a history of breast cancer, but an assessment of the effect of estrogen exposure (e.g., pregnancy, oral contraceptive use, HRT use) on prognosis showed that estrogen exposure did not confer a worse prognosis.[47] The American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice and the Eastern Cooperative Oncology Group have both suggested that estrogen replacement therapy (ERT) may be appropriate for some women previously treated for breast cancer.[47,48]

Endometrial Cancer

Endometrial cancer is the third most common cancer among women in the U.S. Unopposed (taken alone) estrogen substantially increases the risk for development of endometrial cancer. Based on the pooled results of 35 studies, the risk of endometrial cancer is 2.3 times greater among women who have used ERT than among those who have never used estrogen.[7] Women who used ERT for 10 years or longer were almost ten times more likely to develop endometrial cancer than women who never used estrogen. The increased risk also persists for five or more years after stopping estrogen therapy.[49]

The PEPI trial reported that within 3 years, 62% of women on unopposed estrogen developed some type of endometrial hyperplasia, which is considered a possible precursor to endometrial cancer. In contrast, the rate of hyperplasia among women on estrogen/progestin regimens was similar to that in women taking a placebo.[50] Therefore, women who take postmenopausal estrogen and have an intact uterus should use it in conjunction with a progestin to avoid the increased risk for endometrial hyperplasia and cancer. If a woman cannot tolerate progestins, an annual endometrial biopsy is recommended. If hyperplasia develops, estrogen therapy should be stopped and prolonged progestin therapy administered in an attempt to cause the endometrium to revert to normal.[50]

Breast Cancer

Breast cancer is the most common cancer in women. A 50 year old white woman has a 10% chance and a 50 year old African American woman a 7% chance of developing breast cancer during the remainder of her life. Among women with a mother or sister who has had breast cancer, the risk is increased to about 20%. The median age for breast cancer diagnosis is 69 years.[4,7] Prolonged exposure to endogenous estrogen (as may occur in women who begin menstruation at a young age, bear no children, or experience a late menopause) is associated with an increased risk for breast cancer. Thus, it is possible that postmenopausal hormone therapy also increases the risk of breast cancer. Recent studies have shown that long-term users of postmenopausal hormones (>9 years) have a 1.3-1.5 times greater risk of breast cancer than women who do not use HRT.[4,51,52] In addition, there is some evidence that the combination of estrogen and progestin may increase the risk for breast cancer more than unopposed estrogen.[4] Short-term therapy (less than 5 years of use) is associated with little increase in risk. Previous use also seems to result in little increase in risk, once therapy has been discontinued for several years.

Common Adverse Effects

Side effects are not uncommon with HRT, but are severe in only 8-14% of women.[53] Side effects can often be related to one of the hormones.[54] Common estrogen-related adverse effects are nausea, breast tenderness,

heavy withdrawal bleeding, and headaches. Side effects related to progestins include bloating and mood changes. A decreased libido may result from insufficient androgen. Modification of the hormonal components is the usual technique for managing common adverse effects (see Table 1).

Transdermal patches can cause skin irritation and itching. Rotating the site of patch application helps minimize this problem. If skin irritation occurs, applying the patch to a less sensitive area (e.g., buttocks or thighs rather than abdomen) or air-drying the patch for a minute prior to application may help.[54] Education about common side effects and the need to adjust therapy can help decrease patient frustration and ensure long-term use. When HRT is stopped, the dosages should be tapered slowly over several months to avoid an increase in menopausal symptoms.[55]

Summary

Postmenopausal hormone therapy has the potential to provide significant health benefits, but those benefits are accompanied by several health risks. It is clear that HRT does not benefit all women to the same extent. In particular, women at low risk for CHD gain less benefit than those at high risk or women with diagnosed CHD. Identifying women for whom the potential benefits exceed the risks is the challenge of ERT/HRT utilization. Risk-benefit assessment must evaluate each woman's health information in conjunction with the data available from observational studies and clinical trials. Pharmacists can help women faced with this decision by explaining the data in the medical literature so that it is meaningful to them. In addition, pharmacists can help women and prescribers tailor therapy in order to minimize side effects. Finally, pharmacists should encourage women to follow the national recommendations for breast cancer screening and discuss any unexpected side effects of HRT, including bleeding, with their prescriber. ■

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DIRECTIONS FOR OBTAINING CE:

Read the article and take the test below to receive three (3) hours of continuing education credit. Return the entire test page and include a self-addressed, stamped envelope. Please note that the passing grade is 70%. If necessary, one test will be readministered.

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ACPE Universal Program No. 126-113-98-007-H01

This is to certify that the above-mentioned continuing education course was completed by:
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You successfully passed with a score of: _____ percent.

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Test Questions

1. Nonprescription NSAIDs can be recommended to women suffering from either primary or secondary dysmenorrhea
a. True
b. False

2. The following is not a correct recommendation to a patient:
a. An initial dose of naproxen 440mg can be taken for symptom relief.
b. The dose and type of NSAID can be varied every 3-6 months as needed.
c. NSAIDs should only be taken on an as needed basis.
d. If NSAIDs do not provide relief, the patient should see the physician about prescription therapy (e.g. birth control pills).

3. Which of the following symptoms does not indicate primary dysmenorrhea?
a. Onset of symptoms at 32 years of age.
b. Symptoms are especially bad on the first day of menses.
c. Maximum does of ketoprofen did not relieve symptoms.
d. None of the above indicate primary dysmenorrhea.
e. A and C

4. According to the article, some clinicians advocate the use of which SSRI for use in breastfeeding?
a. Fluoxetine
b. Sertraline
c. Paroxetine
d. Fluvoxamine
e. All of the above

5. Which of the following are most likely to cause sexual dysfunction in women?
a. Tricyclic antidepressants
b. SSRIs
c. MAO inhibitors
d. Buproprion

6. Menopause and pregnancy are both likely to affect antidepressant pharmacokinetics.
a. True
b. False

7. There is a window of safety for drug exposure from the first day of the last menstrual period through.
a. Four days post-conception
b. One week post-conception
c. Two weeks post-conception
d. Three weeks post-conception

8. The following should be asked of a patient concerned about taking a medication while breastfeeding:
a. Dose of the drug
b. Schedule/regimen
c. Duration of therapy
d. Age of the infant
e. All of the above

9. Which of the following is not a reason to refer a patient to the physician for treatment of a vaginal yeast infection?
a. Patient is pregnant
b. Patient is diabetic
c. Patient has had three previous yeast infections
d. Patient had a yeast infection last month
e. All of the above are reasons to refer

10. Which of the following statements is incorrect?
a. Concurrent use of an antifungal agent and contraception foam can decrease the effectiveness of both agents.
b. It is OK to use a sanitary napkin during menses while using a vaginal antifungal product.
c. The use of a condom and a diaphragm should be avoided for 72 hours after itra conazole therapy.
d. Tioconazole is the best choice for someone who has had a vaginal yeast infection within the last six months.
e. Both C and D are incorrect.

11) The feature which distinguishes yeast infections from bacterial infections is:
a. Burning with urination
b. Urinary frequency
c. Absence of offensive odor from discharge
d. Itching

12) The most cost-effective pharmacotherapy for preventing and treating osteoporosis in postmenopausal women is:
a) alendronate
b) hormone replacement therapy
c) calcitonin
d) fluoride
e) etidronate

13) Estimated national direct expenditures for osteoporosis and related fractures, including the cost of hospitalization, surgery, and nursing home care are:
a) 1 million dollars per year
b) 1 billion dollars annually
c) 5 billion dollars annually
d) 10 billion dollars annually
e) none of the above

14) All of the following are risk factors for coronary artery disease in women, except:
a) smoking
b) diabetes
c) hypertension
d) increased estrogen levels
e) elevated cholesterol

15) All of the following statements are true except:
a) Nitrates are not as effective in reducing the frequency or intensity of anginal symptoms in women as they are in men with chronic stable angina.
b) The long term outcome after percutaneous transluminal coronary angioplasty is better for women than for men.
c) Women are more likely to be referred to cardiac rehabilitation programs than men.
d) A recent study demonstrated an increase in 10 year survival from 60% to 70% in women with coronary artery disease on hormone replacement therapy compared to women with coronary artery disease who were not on hormone replacement therapy.
e) The incidence of coronary artery disease in women increases dramatically after menopause.

16) Contraindications to the use of hormonal contraceptive agents include:
a) current thromboembolic disorders
b) a history of hormone sensitive tumors
c) a desire to become pregnant
d) all of the above

17) Non-contraceptive benefits of oral contraceptives include:
a) protection from ovarian and endometrial cancer
b) decreased risk of rheumatoid arthritis
c) reduced risk of ectopic pregnancy
d) improved cycle control
e) all of the above

18) The American Cancer Society recommends a baseline mammogram at the age of:
a) 35
b) 50
c) 40
d) 60
e) 30

19) Patients diagnosed with breast cancer are most likely to benefit from chemotherapy if they present as:
a) Post-menopausal, hormone receptor positive, and node-positive
b) Pre-menopausal, hormone receptor negative, and node-negative
c) Post-menopausal, hormone receptor positive, and node-negative
d) Elderly and hormone receptor positive
e) Pre-menopausal, low risk, and node-negative

20) Use of paclitaxel requires the patient to be pre-medicated with dexamethasone, cimetidine, and diphenhydramine prior to chemotherapy administration:
a) True
b) False

21) What is the single most predictable indicator of long-term prognosis?
a) Size of tumor
b) Location of tumor
c) Number of malignant nodes
d) Hormone receptor status
e) Type of tumor

22) At the time of initial diagnosis, what percent of patients will already have advanced stage ovarian cancer?
a) 5-10%
b) 30-40%
c) 50-60%
d) 60-70%
e) 80-90%

23) Which of the following chemotherapy regimens is considered first-line therapy for ovarian cancer?
a) Cisplatin + carboplatin
b) Cisplatin + paclitaxel
c) Cisplatine + cyclophosphamide
d) Carboplatin + cyclophosphamide
e) Topotecan

24) Which of the following is not a side effect of cisplatin?
a) Neurotoxicity
b) Nephrotoxicity
c) Cardiotoxicity
d) Ototoxicity
e) Nausea and vomiting

25) Which of the following new chemotherapeutic agents is approved for the use as a secondline agent for ovarian cancer?
a) Gemcitabine
b) Docetaxel
c) Topotecan
d) Liposomal Doxurubicin

Making a Difference

The Rx Consultant

For demonstrating the value of communication and the importance of serving the patient education needs of today's pharmacist, we extend a special thanks to Terry M. Baker, Pharm. D, Editor of *The Rx Consultant*, who assisted in the editing and organizing of this issue of *Health Notes*.

The Women's Health Issue Editorial Panel

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